

**DIURNAL INTRA OCULAR PRESSURE PROFILES IN PATIENTS WITH  
OPEN ANGLE GLAUCOMA WHO HAVE UNDERGONE  
TRABECULECTOMY VERSUS THOSE ON TOPICAL OCULAR  
HYPOTENSIVE MEDICATION**



**DISSERTATION SUBMITTED AS A PART OF FULFILMENT FOR THE  
BRANCH III (OPHTHALMOLOGY) DEGREE EXAMINATION OF THE  
TAMIL NADU DR. M.G.R MEDICAL UNIVERSITY,  
TO BE HELD IN MAY 2018**

**Dr. M.G.R. UNIVERSITY, CHENNAI**

**To be held in 2018**

**DECLARATION BY THE CANDIDATE**

This is to declare that the dissertation entitled “Diurnal intra ocular pressure profiles in patients with open angle glaucoma who have undergone trabeculectomy versus those on topical ocular hypotensive medication” is my original work towards partial fulfilment of MS (Ophthalmology) Branch III Examination of the Tamil Nadu Dr. M.G.R. University, Chennai, to be held in 2018.

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## **BONA FIDE CERTIFICATE**

This is to certify that this dissertation entitled “Diurnal intra ocular pressure profiles in patients with open angle glaucoma who have undergone trabeculectomy versus those on topical ocular hypotensive medication” done towards fulfilment of the requirements of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for the MS Branch III (Ophthalmology) examination to be conducted in May 2018, is a bona fide work of Dr. Roshni J, post graduate student in the Department of Ophthalmology, Christian Medical College, Vellore.

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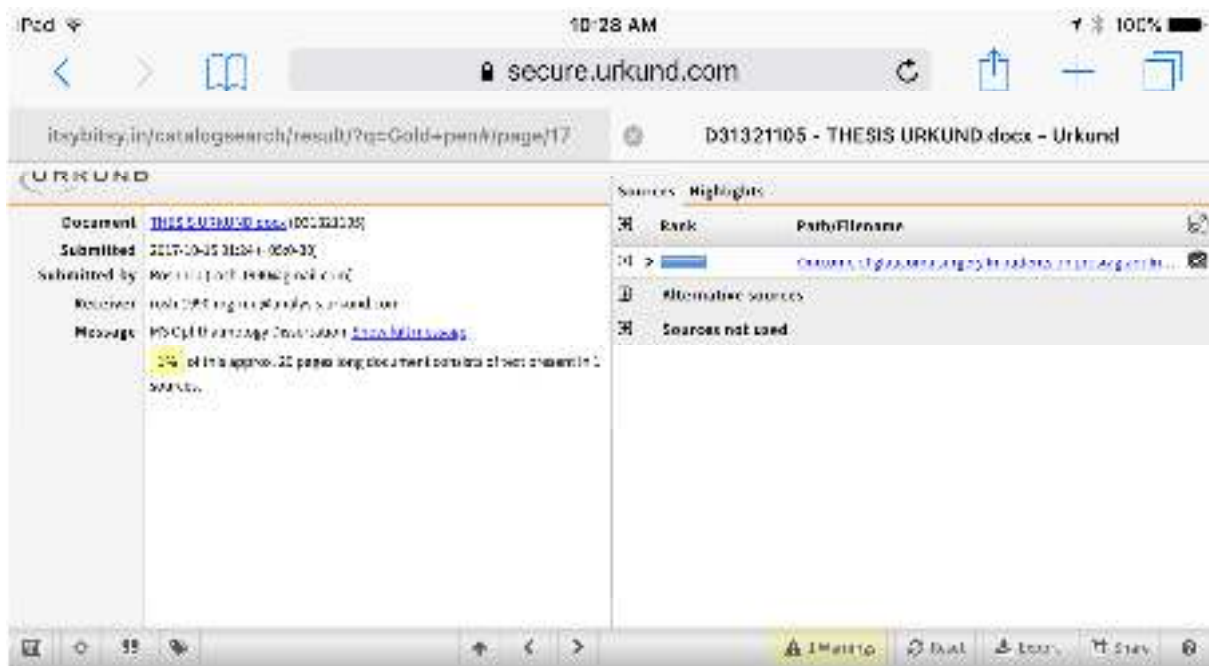
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Dr. Lekha Mary Abraham, Professor

## ANTI PLAGIARISM CERTIFICATE I



INTRODUCTION

Type the link in the address bar. The address is [http://www.fishbase.org/summary/summary.cfm?table=tbl\\_descend](http://www.fishbase.org/summary/summary.cfm?table=tbl_descend). You should see a list of the phylogeny keys. The table is displayed in a hierarchical way, by category of fish (class, order, etc.).

Heart failure (HF) can occur as a result of any disease of the heart, with a common cause being a history of coronary artery disease that has led to the development of coronary artery disease and atherosclerosis. HF can have many different causes, but it is often the result of atherosclerosis. In the United States, HF is the most common cause of death, and it is the leading cause of hospitalization. HF is a chronic condition, and it is often managed with medication and lifestyle changes. The goal of treatment is to improve the patient's quality of life and to prevent further complications. HF can be a challenging condition to manage, but with the right treatment and support, many patients can live well with the condition.

While acknowledging that the extent of the disturbance was moderate, the panel also noted that the proposed development was not a "major project" under the CEQA. The panel stated that the proposed development was not a "major project" under the CEQA because it did not meet the criteria for a "major project" under the CEQA. The panel stated that the proposed development was not a "major project" under the CEQA because it did not meet the criteria for a "major project" under the CEQA.

The overall effect of the study design on the estimated magnitude of the effect depended on the number of sectors of the housing, garden and street needed to be visited to experience the perceived environmental quality improvement. The estimated effect was smaller in the follow-up study (0.02) and the effect sizes were smaller in the study of the same intervention in the same population in a different location (0.01) than in the stepped wedge trial (0.03). The magnitude of the perceived improvement in the quality of the housing, garden and street was not significantly different between the two studies. The results of the present study are different from the results of the other studies in that the effect of the intervention was smaller in the follow-up study than in the stepped wedge trial.

## **ANTI PLAGIARISM CERTIFICATE II**

This is to certify that the dissertation work titled “Diurnal intra ocular pressure profiles in patients with open angle glaucoma who have undergone trabeculectomy versus those on topical ocular hypotensive medication” has been submitted by the candidate Dr. Roshni J with registration number 221513305, for the award of the degree of MS Ophthalmology Branch III. I have personally verified the urkund.com website for the purpose of plagiarism check. I have found that the uploaded thesis file contains from introduction to conclusion and that the result shows ONE percentage plagiarism in the dissertation.

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Diurnal intra ocular pressure profiles in patients with open angle glaucoma who have undergone trabeculectomy versus those on topical ocular hypotensive medications.  
Dr. Roshni J, Employment Number: 29493, PG Registrar Dr. Arathi Simha, Employment Number: 20217, Dr. Lekha Mary Abraham – Professor, Employment number: 20086, Dr. Andrew David Braganza – Professor, Employment Number: 14092, Department of Ophthalmology. Ms Reka K, Senior Demonstrator, Department of Biostatistics.

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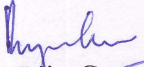
Dear Dr. Roshni J,

I enclose the following documents:-

1. Institutional Review Board approval
2. Agreement

Could you please sign the agreement and send it to Dr. Biju George, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

  
Dr. Biju George  
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Dear Dr. Roshni J,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled “Diurnal intra ocular pressure profiles in patients with open angle glaucoma who have undergone trabeculectomy versus those on topical ocular hypotensive medications” on January 05<sup>th</sup> 2017.

The Committee reviewed the following documents:

1. IRB Application format
2. Patient Information Sheet
3. Data Sheet
4. Cvs of Drs. Lekha Mary, Andrew Braganza and Arathi Simha
5. No. of documents 1 - 4.

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on January 05<sup>th</sup> 2017 in the BRTC Conference Room, Christian Medical College, Bagayam, Vellore 632002.

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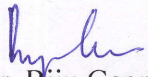
We approve the project to be conducted as presented.

Kindly provide the total number of patients enrolled in your study and the total number of withdrawals for the study entitled: "Diurnal intra ocular pressure profiles in patients with open angle glaucoma who have undergone trabeculectomy versus those on topical ocular hypotensive medications." on a monthly basis. Please send copies of this to the Research Office ([research@cmcvellore.ac.in](mailto:research@cmcvellore.ac.in)).

Fluid Grant Allocation:

A sum of 45,600/- INR (Rupees Forty Five Thousand Six Hundred Only) will be granted for 12 months.

Yours sincerely,

  
Dr. Biju George  
Secretary (Ethics Committee),  
Institutional Review Board  
IRB Min. No. 10478 [OBSERV] dated 05.01.2017

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## ACKNOWLEDGEMENTS

At the outset, I thank the Lord Almighty for making all things possible in all circumstances.

I offer my heartfelt gratitude to my guide, for her constant support and encouragement from the start to the finish.

I acknowledge with gratitude each patient who participated in this study. Without their efforts, this study would not have been possible.

To my family and friends- a very warm thanks for all your encouragement, help and humor when needed.



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## INTRODUCTION

Glaucoma is defined as a disturbance of the structural or functional integrity of the optic nerve that can usually be arrested or diminished by adequate lowering of IOP.(1) The term does not refer to a single disease entity, but rather to a group of diseases that differ in their clinical presentation, pathophysiology, and treatment. These diseases are grouped together because they share certain features, including cupping and atrophy of the optic nerve head, which has attendant visual field loss and is frequently related to the level of intraocular pressure (IOP).

The pathophysiology of glaucoma is a much- studied topic. Normal intraocular pressure is maintained by the production and drainage of aqueous humour, which circulates within the anterior chamber. The primary glaucomas are not associated with known ocular or systemic disorders that account for the increased resistance to aqueous outflow; the primary diseases are usually bilateral and probably reflect genetic predispositions.(2) Conversely, the secondary glaucomas are associated with ocular or systemic abnormalities responsible for elevated IOP; these diseases are often unilateral and acquired. Although many risk factors have been associated with the development of POAG – including thinner central corneal thickness, myopia, age, African or Hispanic race and diastolic perfusion pressure, elevated IOP remains the most prominent factor – shared among the primary and secondary glaucomas – and the only factor that ophthalmic intervention can reliably modify.

That lowering the intraocular pressure can reduce the progression of glaucoma has been shown by multiple studies.(3,4) The Advanced Glaucoma Intervention Study

has shown that every 1 mm hg lowering of IOP reduces the risk of progression of glaucoma by 10%. Hence lowering of the intraocular pressure through medical or surgical means remains the mainstay of glaucoma therapy.

The decision of primary surgical versus medical management would depend on a number of factors. For instance, patients who would be unlikely to respond adequately to conventional medical treatment, including those unavailable for follow-up, unable to instil eye drops, or those with local ocular conditions that preclude the use of long-term topical medications (such as atopy or benign mucous membrane pemphigoid); patients in whom a target IOP level is unlikely to be achieved with topical medications, because the baseline pressure lies at either end of the open-angle glaucoma spectrum (12-19 mm Hg or >35 mm Hg), and patients with visual field loss such that any further progression would affect the patient's quality of life, would benefit from surgery as the primary intervention.(5) In a study done by Xiau H. et al(6) to evaluate the changes of optic disc parameters in primary open angle glaucoma patients after surgical and medical treatment, it was found that improvement in optic disc parameters occurred more commonly after surgical than medical treatment. The amount of reduction of IOP correlated with the extent of this improvement.

In normal individuals, IOP fluctuates 2 to 6 mmHg over a 24 hour period.(7) Drance(8) first characterized the diurnal patterns in IOP, and found that pressures were higher in the early morning than later in the day. Subsequent investigators examined the 24-hour pattern of IOP and found that nocturnal IOP was lower than diurnal IOP when measured in the sitting position.(9) However, when IOP is measured in the usual physiologic positions of sitting while awake and supine during



sleep, Liu and co-workers(10) demonstrated that IOP was significantly higher during the nocturnal period than the diurnal period. Among individual subjects, two-thirds of glaucoma patients and over 90% of healthy controls had IOP peaks during the nocturnal period.(11) This diurnal variation in IOP Has been attributed to various causes, including postural variation,(12) circulating catacholamines(13) and increase in episcleral venous pressure. A study by Quaranta et al(14) found that the mean peak in IOP curves for young healthy individuals was found to occur in the early morning hours (between 5:30 AM and 6:30AM) depending on body posture. Another study by Mansouri et al(15) for older healthy individuals at around 10:00 AM irrespective of body posture, while that in untreated glaucomatous patients was generally between 6 AM and 10 AM.

In the eyes of patients with open angle glaucoma, the range of diurnal fluctuation has been found to be exaggerated to around 10 mm of Hg, or even up to 30-35 mm of Hg.(8,16) In a study conducted by Wilensky et al,(17) it was found that more than half of a group of patients with seemingly well controlled IOPs of 21 mm Hg or less in the office who were evidencing some progression of their visual field defects had pressure spikes greater than 22 mm Hg when diurnal curves were plotted using a self tonometer. Moreover, 50% of the time, the highest pressure was measured outside office hours. Another study conducted by Asrani et al(18) employed self tonometry at home to arrive at similar conclusions. The study concluded that in patients with glaucoma with office IOP in the normal range, large fluctuations in diurnal IOP are a significant risk factor, independent of parameters obtained in the office.

There are very few studies comparing the peak lowering effect of trabeculectomy versus that of topical anti glaucoma medication. One such study conducted by Ross AH et al(19) at the Bristol Eye Hospital, United Kingdom was an observational study, comparing a group of patients who underwent trabeculectomy and another group on medical management. It was concluded that although there was no significant difference between the IOP fluctuations among the 2 groups, the mean IOP was lower in the surgical group.

Another study conducted by Konstas et al(20) aimed to evaluate 24-hour intraocular pressure control in patients with moderate to severe open-angle glaucoma treated by trabeculectomy and mitomycin C versus maximum tolerated medical therapy. In a comparison of the diurnal IOP curves among the two groups, it was found that the surgical group had a lower peak and mean IOP, and also a significantly lower fluctuation of 24 hour IOP. The majority of peak IOPs (10 of 11) occurred outside of normal office hours. This study concluded that a well-functioning trabeculectomy provides a statistically lower mean, peak, and range of IOP for the 24-hour day than maximum tolerated medical therapy in advanced glaucoma patients.

In spite of evidence that diurnal fluctuations in intraocular pressure play an important role in the progression of glaucoma, this remains a topic of debate among glaucoma experts.(21) We conducted this study as very few studies,(20,22) and notably no studies comparing the diurnal intraocular pressure profiles in surgically and medically managed patients have been conducted in India.

## AIM

To compare the diurnal intraocular pressure profiles in patients with open angle glaucoma with intraocular pressure controlled on medical management (ocular hypotensive medication) versus those with intraocular pressure controlled following trabeculectomy.



## **OBJECTIVES**

### **Primary objectives:**

1. To compare the mean and peak intraocular pressures during a phased 24 hour recording of intraocular pressure in patients with open angle glaucoma with intraocular pressure controlled on medical management versus those with intraocular pressure controlled following trabeculectomy.

2. To compare the fluctuation of intraocular pressure variation during a phased 24 hour recording of intraocular pressure in patients with open angle glaucoma with intraocular pressure controlled on medical management versus those with intraocular pressure controlled following trabeculectomy.

### **Secondary objectives:**

1. To determine the timings of peak intraocular pressures in the two groups
2. To plot and compare the diurnal intraocular pressure curves in the two groups
3. To measure supine nocturnal intraocular pressure using Tonopen and assess its significance.

## REVIEW OF LITERATURE

### INTRODUCTION

Glaucoma can be defined as a structural or functional disturbance in the integrity of the optic nerve that can usually be arrested or diminished by adequate lowering of IOP.(1) It is a chronic progressive optic neuropathy resulting in the gradual loss of peripheral vision and later, the central vision, leading to eventual blindness.(2) It is not a single disease, but rather a group of entities that share certain common pathological characteristics. The aetiology and pathogenesis of the glaucomas have been the subject of intensive study; however, they are yet to be fully understood.

The open angle glaucomas may be classified as primary or secondary. Primary open angle glaucoma (POAG) is the commonest form of glaucoma in many countries. It was estimated that 45 million people suffered from this disease worldwide in the year 2010.(23) Because POAG is a chronic, slowly progressive insidious disease, individuals are asymptomatic until very late in the disease course; hence they may seek help only in advanced stages of the disease. Especially in developing countries, due to the scarcity of ophthalmological care and limited access, glaucoma is often diagnosed very late.(24)

Multiple risk factors have been associated with primary open angle glaucoma, including older age,(25) African race(26), myopia, lower central corneal thickness(27), family history of glaucoma(27), genetic factors(28), and high intraocular pressure(27). Among all these, intraocular pressure has been identified as the only modifiable risk factor.

## EPIDEMIOLOGY AND BURDEN OF DISEASE

The glaucomas together constitute the second leading cause for blindness globally, following cataracts, and the leading cause for irreversible blindness.(29) The overall prevalence of glaucoma was around 3·5% for people aged 40–80 years, globally. This was estimated to be 64.3 million people in 2013, and is expected to rise to 76.0 million in 2020.(23) Out of these, 56 million will be suffering from open angle glaucoma.

In India, different studies have been done to estimate the prevalence of glaucoma in the population. According to the Andhra Pradesh Eye Disease Study, the prevalence of Primary Open Angle Glaucoma (POAG) in a rural south Indian population was found to be 1.62%.(30) The Chennai Glaucoma Study was conducted among two groups- rural and urban; it was found that the Urban population had a higher prevalence of POAG (3.51%) as compared to the rural population (1.62%).(31)The Vellore Eye Study found a prevalence of POAG of 0.41% and a higher prevalence of primary angle closure glaucoma of 4.32%.(32) The prevalence of angle closure glaucomas have also been found to be higher in Asians and Inuit Indians, However, in most other populations, open angle glaucomas have been found to be more prevalent.

Open angle glaucomas are characteristically symptomless- patients do not experience any ocular pain or vision loss in the earlier stages. They are either detected to have glaucoma incidentally, which may be relatively early in the course of disease, or, after vision loss is noticed by the patient, which may be at a much later stage when significant and irreversible glaucomatous damage has already occurred. In developing

countries, where a large fraction of the population is rural and the majority of healthcare facilities are concentrated in urban areas, access to healthcare for a large section of the population is very poor. This leads to a delayed diagnosis of glaucoma and hence poor visual outcomes.(33)

## MECHANISM OF AQUEOUS SECRETION AND OUTFLOW

The aqueous humour is a transparent fluid secreted by the ciliary processes of the eye. This serves the primary role of nourishing the cornea and the crystalline lens, which are avascular structures. This constant nourishment and removal of wastes is necessary to maintain the transparency of the ocular media. There is a constant production and outflow of aqueous. The force responsible for the drainage of aqueous depends on the hydrostatic pressure across the outflow routes. The combination of aqueous secretion, aqueous outflow and resistance to aqueous outflow ensures a relatively high pressure within the globe, known as the intraocular pressure (IOP). This is a necessary requirement to maintain a stable globe, even with the traction forces exerted by the extra ocular muscles.(34)

The formation of aqueous involves two main steps. The first is ultrafiltration of the plasma through the semi permeable walls of the capillaries of the ciliary processes. This results in the formation of a scanty protein rich ultra filtrate which contains about 60% of plasma protein. The second step involves active transport of sodium by the non pigmented layer of the ciliary processes. This is followed by an efflux of negative ions, including bicarbonate, from within the cell into the intercellular cleft. This results in a strong osmotic gradient which also results in the efflux of water molecules

into the extracellular space. Nutrients and other substances necessary for survival of the lens and cornea bypass the blood aqueous barrier and are transported by free or facilitated diffusion.(1),(34)

The normal rate of aqueous production was determined to be  $2.75 \pm 0.63$  microliters per minute. The rate of aqueous flow also showed a distinct circadian rhythm, with the lowest flow of 1.2 microliters per minute seen between 12 midnight and 6 am. Other than the circadian rhythm, no other factors were found to significantly affect the pattern of aqueous secretion. (35)

## MEASUREMENT OF INTRAOCULAR PRESSURE

There are several available instruments for the measurement of intraocular pressure. They can be broadly classified into applanation instruments, indentation instruments, dynamic contour tonometry and instruments for the continuous measurement of IOP.(1) Applanation tonometry is the most commonly performed technique- the Goldmann Applanation tonometer being considered the gold standard in IOP measurement. The TonoPen is a portable applanation tonometer which provides a digital display of the measured IOP. Indentation tonometers include the Schiotz tonometer, which is not widely used now. Dynamic contour tonometry is used mainly in research settings. Contact lens sensors which measure IOP through the measurement of ocular dimensional changes have also been used in a few studies and provide a continuous recording of IOP.(36)

Studies have been performed to assess the comparability of different techniques of IOP measurement. Bhartiya et al(37) conducted a study among 50 glaucomatous



and 130 normotensive eyes of a total of 180 patients comparing the IOP as measured by non contact tonometry (NCT), Goldmann applanation tonometry (GAT) and with TonoPen Avia (TPA). The limits of agreement (confidence interval 95%) for TPA–GAT and TPA–NCT were +8.7 to –7.7 and +8.6 to –9.6 mmHg in the glaucomatous patients. In healthy subjects the limits were +4.8 to –5.1 and +6.2 to –5.2 mmHg, respectively. TPA was found to overestimate IOP compared to GAT in eyes with a central corneal thickness (CCT) greater than 520  $\mu\text{m}$  and underestimate IOP in eyes with CCT less than 510  $\mu\text{m}$ .

Another study by Kurtz et al(38) compared the IOP in patients with normal tension glaucoma as measured by three modalities- dynamic contour tonometry (Pascal-DCT), Goldmann applanation tonometry (GAT) and Tonopen XL. They found that the mean DCT IOP was higher than the mean GAT IOP by 3.07 mm, whereas the mean Tonopen IOP was lower than the mean GAT IOP by 0.7 mm Hg.

## INTRAOCULAR PRESSURE AND ITS VARIATION

### **Normal range of intraocular pressure**

The intraocular pressure in healthy humans has been found to have a mean of 15.5 mm Hg in large population based studies, with a standard deviation of 2.6 mm Hg. (39) Thus, the normal intraocular pressure has been defined to be a range two standard deviations above and below the mean, that is,  $15.5 \pm 5.2$  mm Hg, which is 10- 21 mm Hg. Jonas et al,(40) conducted a study done in rural areas in Nagpur, central India. 9338 normal eyes of 4686 patients were tested. The age of patients ranged from 30 to 100. The mean IOP was found to be around  $13.6 \pm 3.4$  mm Hg. It

must be remembered that although this has been defined as the “normal” range of intraocular pressure, in some patients, glaucomatous changes have been found even with pressures within this range.(41) Conversely, some individuals do not show any glaucomatous changes even with pressures higher than this range.(42)

### **Variation of intraocular pressure**

The intraocular pressure is not maintained at a constant value; it has been found to fluctuate in both non glaucomatous and glaucomatous individuals. This was recognised as early as 1899, when Huguenin reported variation in tactile tension. This was confirmed by Maselnikov in 1904, using applanation tonometry. The dynamics of aqueous humour secretion and outflow have been studied extensively. It has been found in studies that the secretion of aqueous humour is reduced at night, even by up to 50%, and also that aqueous outflow is slightly reduced.(43) In spite of the significant reduction in aqueous outflow, repeated studies have revealed consistent peaks of IOP in the night time. There are different postulated mechanisms regarding the fluctuation of IOP. Thomassen(44) and Bain(45) showed that the nocturnal rise in IOP was preceded by a recordable elevation in the episcleral venous pressure. Previous studies have shown that impairment of the sympathetic system abolishes the circadian rhythm of IOP, implicating adrenergic stimulation in the fluctuation pattern. Other studies have shown that exposure to short wavelength light abolishes the IOP curve.(16) Additionally, melatonin, which is secreted locally by the ciliary body with a night time peak, has also been postulated as a causative factor.(46)

## **Variation of intraocular pressure with posture**

An important factor that can change the IOP is body posture; generally, IOP measured in the sitting position is lower than that measured in supine position.

A diurnal study performed by Chiquet and co-workers(47) showed that sitting IOP was significantly lower than supine IOP, with a mean pressure difference of  $2.2 \pm 2.9$  mmHg after 1 min and  $1.9 \pm 3.8$  mmHg after 10 min of posture change. However, after performing similar measurements with a head lowering bed tilts, the eyes exhibited an eventual slight decrease of IOP of 1.3 mmHg as compared to the initial supine IOP.

In a study conducted by Liu et al(48), 24 hour IOP measurements were performed on 33 volunteers who were housed in a sleep laboratory for a 24 hour period under a controlled 16-h light and 8-h dark environment. The IOP was measured every 2 hours using a pneumatonometer. In the first part of the study, IOP measurements were performed on 12 volunteers who were seated during the light-wake period and in supine position during the dark period. It was found that the nocturnal/supine IOP was higher than diurnal/seated IOP, with the 24 hour fluctuation of IOP as high as  $8.2 \pm 1.4$  mmHg. This was initially thought to be due to a rise in episcleral venous pressure and redistribution of fluid in the supine position. However, in the latter part of the study, 24 hour IOP measurements were performed on 21 subjects who were kept perpetually in supine position. The mean IOP was still found to be higher in the dark period than the light period, showing that factors besides episcleral venous pressure were at play during the nocturnal period, causing the rise in IOP. This study also found that mean nocturnal IOP measurements were higher as

compared to diurnal IOP levels, both in aging healthy patients and in untreated open-angle glaucoma patients.

In another study by Liu et al(49), the phased 24 hour readings were performed on 18 healthy volunteers. The nocturnal IOPs were measured in sitting position to assess whether posture played a role in the occurrence of nocturnal peaks. It was found that night time IOPs showed peaks similar to those that occur in supine position. It was concluded that posture does not play a role in the occurrence of nocturnal IOP peaks.

Piven et al(50) conducted a study in 41 patients with untreated ocular hypertension or suspicious discs. The IOP was measured by Goldmann Applanation Tonometry in the seated position at 9 AM, 12 AM, 3 PM, and 6 PM; and in right lateral decubitus position around 12:15 PM. It was found that in 91.5% of eyes, the IOP was higher in lateral decubitus position. The right eye showed a raise in IOP of  $4.22 \pm 2.67$  mm Hg and in the left eye,  $3.51 \pm 3.11$  mm Hg. This was significantly higher in the lower eye. The IOP was raised by 2 to 5 mm Hg in 67% of patients and 6 to 12 mm Hg in 23.2% of patients. In the great majority of the eyes (80.5% RE and 78% LE) the lateral decubitus IOP was greater than maximal diurnal sitting IOP.

### **Diurnal variation of IOP in normal individuals:**

Measurement of IOP (tonometry) over a 24 hour period comprises diurnal (daytime) and nocturnal (night time) readings. In most non glaucomatous individuals the IOP shows a diurnal range with peaks in the morning and troughs in the evening and night

In non glaucomatous individuals, IOP fluctuates during a 24 hour period by around 4–6 mmHg.(51) In patients with ocular hypertension, the diurnal fluctuation is about 6–8 mmHg, but can reach as high a level of fluctuation as 15mm Hg. In glaucomatous individuals, the 24-h diurnal variation in IOP ranges between 6 and 15 mmHg, but reaching up to about 40 mmHg in extreme cases.(52) In most patients with glaucoma, 24 hour IOP studies have found that there is an early morning peak in IOP between 6:00 am and 12:00 pm.(53) This is accounted for by the fact that aqueous synthesis is significantly reduced at night, during sleep. However, IOP peaks can occur at any time of the day or night. This may also depend on the type of glaucoma and the number of measurements of IOP taken, with the greater number of IOP measurements giving a more accurate idea of the timing of the peak IOP.

In a study done by Drance et al, the IOP of 404 normal eyes was measured 6 times between 6:00 am and 10:00 pm. It was found that 16% had a range of IOP more than 6 mmHg, while 42% of patients showed a peak in IOP at 6:00 am. The mean range of IOP was  $3.7 \pm 1.8$  mmHg.(54)

In a similar study, Katavisto et al found that the highest IOP values were recorded at 8.00 am in 41% and at midnight in over 20% of 50 normotensive subjects. The mean 24 hour fluctuation of IOP was 3.17 mmHg.(55)

In a study by David et al(16) diurnal IOP measurements were performed in healthy eyes and 690 diurnal curves were analysed. It was found that 40.5% of subjects had an early morning peak, 22.6% at mid-morning, and 19% at mid day.



Newell and Krill et al(56) also studied a normotensive group of 30 individuals and found that the greatest frequency of peak IOPs were measured between 6:00 and 8:00 am.

#### RATIONALE FOR PERFORMING DIURNAL IOP STUDIES IN GLAUCOMA

As stated earlier, intraocular pressure has been found to be the only modifiable risk factor for the prevention of progression of glaucoma. Hence, the mainstay of glaucoma therapy consists in lowering the intraocular pressure to a pre determined target intraocular pressure. (57) The maintenance of the IOP within the target range of IOP is crucial to the management of glaucoma. The IOP is routinely assessed in outpatient settings by various methods of IOP measurement, such as Goldmann applanation tonometry, or the Tonopen. Older methods such as the schiotz tonometer are not used in most clinics now. IOP measurement usually involves a single of few measurements taken during office hours, initially before treatment to establish a baseline and after the initiation of treatment, to ascertain whether it is within the target range.

Though measurement of IOP within office hours is time saving for the patient and the clinician, it must be remembered that one or a few IOPs do not reflect the IOP variations during the entire day. Since glaucomatous optic nerve damage can occur any time of the day, with fluctuations and peaking of IOP, it is important to ascertain whether the target IOP is being maintained throughout the day, and not merely office hours. The routine standard of care in most outpatient departments involves the measurement of one or a few IOPs during office hours; these cannot reflect the entire

IOP variation during a 24 hour period. Hence, this data would be insufficient to ascertain whether the target IOP is being met and maintained throughout the day, and thus, whether the treatment instituted is sufficient for the prevention of glaucomatous progression.

In a study among 100 patients with primary adult onset open angle glaucoma by Arora et al(58), 24 hour IOP measurements were performed. The office hour fluctuation was found to be  $4.31 \pm 2.6$  mm Hg, versus a 24 hour fluctuation of  $7.03 \pm 2.69$  mm Hg. The difference was found to be statistically significant. Two thirds of the patients were found to attain peak IOP outside office hours.

A diurnal IOP profiling in patients before and after treatment would be useful in many ways: first, prior to treatment, it provides a good baseline, including a peak and a range of variation, giving the clinician an understanding of the IOP levels at which glaucomatous damage has occurred; second, this gives us an idea of the target IOP to be set. Though 24 hour IOP measurement is not widespread in mainstream clinical practice, it has recently roused interest in research circles, and, like the 24 hour monitoring of blood pressure, has provided valuable data on the fluctuations of IOP in normal and glaucomatous individuals.

Ideally, for each patient with glaucoma, performing a 24 hour IOP measurement would provide information regarding the baseline range and peak of IOP as well as the post treatment diurnal profile, and would aid us in setting target IOPs and assessing the efficacy of treatment. However, this is impractical, time consuming and expensive, and thus not a realistic strategy. However, this can be overcome by

carrying out well designed studies in appropriate patient groups, and the results extrapolated to other patients with glaucoma.

24 hour IOP studies have been used to study the efficacy of various anti glaucoma medications over the last decade. Most studies have stressed on the unreliability of single or office hour IOP measurements. Patients with an apparent well controlled IOP as per office hour measurements may have uncontrolled IOP peaks outside office hours. In a study conducted by Riva and coworkers(59) the long-term 24-h IOP control in travoprost-treated patients with POAG was assessed by performing repeated 24-h IOP measurements over a 5 year period while being treated with travoprost. It was found that the only predictors for treatment failure were the mean pre-treatment 24-h IOP and treated 24-h peak IOP during the 5 year follow-up period.

## VARIATION OF INTRAOCULAR PRESSURE IN OPEN ANGLE GLAUCOMA

Several types of rhythms of intraocular pressure fluctuation have been described in glaucoma. Duke-Elder in 1954 described three types of curves in open angle glaucoma: a downward sloping curve with the peak soon after waking, seen in about 20 per cent patients, an upward sloping curve with the peak between 4:00 pm and 6:00 pm seen in 25 per cent cases, and a biphasic curve with a peak between 9:00 am and 11:00 am, and a second peak between 4:00 and 6:00 pm seen in 55 per cent patients. Other studies have also reported flat curves or irregular curves with frequent peaks, but these are rarer.(60)

The three main features of a 24 hour IOP profile are: (a) the mean IOP, (b) the range of IOP, and (c) the peak IOP. Although the value of 24 hour IOP measurement in the long term treatment of glaucoma is yet to be proven, it has been found that those with uncontrolled IOP peaks show greater worsening.

In a study conducted by Asrani et al, Sixty-four patients (105 eyes with open angle glaucoma, on treatment, all of whom had office hour IOPs less than 25 mm Hg over a follow up period of 5 years, performed home tonometry with a self-tonometer five times a day for 5 days. Although mean home IOP and baseline office IOP were similar ( $16.4 \pm 3.6$  mm Hg and  $17.6 \pm 3.2$  mm Hg, respectively), the IOP range over the 5 days of home tonometry was  $10.0 \pm 2.9$  mm Hg. The diurnal IOP range and the IOP range over multiple days were found to be significant risk factors for progression. The study concluded that large fluctuations of IOP were an independent risk factor for the progression of glaucoma, irrespective of baseline characteristics.(61)

In a study by Konstas et al,(62) it was found that 45% of patients with exfoliation glaucoma and 22.5% of those with POAG showed a peaking of IOP outside of office hours. This re-emphasizes the need for the measurement of IOP outside office hours.

It has been found in various studies that approximately two-thirds of the patients with untreated normal tension glaucoma (NTG) or untreated POAG attain a peak IOP in the morning. David et al.(16) performed a diurnal IOP study and recorded the highest IOP in the early morning hours in 40% of cases, while a further 25% of peak IOPs occurred before 12 pm. The trough IOP was not found to occur at any

particular time of the day. The mean range of IOP was 5.0 mmHg in normotensive subjects, 5.8 mmHg in glaucomatous individuals and 6.8 mmHg in ocular hypertensives.

Wilensky et al.(12) studied 176 patients with POAG, 55 subjects with OHT and 18 normal controls. Self-tonometry was successfully performed at home 5 times daily for 4 to 8 days with a pneumato-tonometer. It was found that each of the groups had well defined IOP curves, and that the peak IOPs occurred in the morning or before midday.

Similarly, Sacca et al(63) performed 2 hourly IOP measurements on 33 healthy volunteers, 95 patients with POAG and 50 with NTG from 8:00 am to 8:00 pm. The morning hours were found to show the maximum number of peak IOPs whereas the trough IOPs were found to occur in the afternoon. The daily IOP fluctuations were directly proportional to IOP levels. The fluctuations were higher in the POAG group (7% to 9.6%) than the control group (3.4% To 6.9%) and the NTG group (4.7% to 6.4%).

Collaer and coworkers(64,65) studied 53 patients with NTG, 12 glaucoma suspects, and 28 patients with POAG and came to similar conclusions as the previous investigators. The characteristics of their diurnal IOP curve performed between 7:00 am and 5:00 pm were similar in all 3 patient groups: higher IOP in the early morning, lower in the early afternoon, and a tendency for pressure to rise again at the end of the afternoon. In this study mean diurnal IOP fluctuation was  $5 \pm 2$  mmHg. In a retrospective chart review study, diurnal IOP measurements of 68 untreated glaucoma suspects and 95 patients with NTG were performed at 10:00 am, 1:00 pm, 4:00 pm,



7:00 pm, 10:00 pm, and 7:00 am. Again in the glaucoma suspects, the peak IOP was noted in the morning: at 7:00 am in the right eye and at 10:00 am in the left eye. The trough IOP was observed at 10:00 pm for both eyes. For both eyes of patients with NTG, the peak IOP occurred at 7:00 am and the trough IOP was measured at 10:00 pm.

It has been found that the diurnal IOP variation between the two eyes in POAG is largely concordant. Dinn et al(66) performed a diurnal IOP study on 93 patients with POAG. IOPs were recorded at 10 am, 1 pm, 4 pm, 7 pm, 10 pm and 7 am the next day. 56 of the 93 patients were treated with symmetric IOP lowering medication in the fellow eye, whereas 37 were not. They noted that the diurnal IOP curves exhibited parallel patterns in the fellow eyes. The IOP in the fellow eye at each time point was within 1.6 to 2 mm of the IOP in the treated eye. There was a 68 to 90 % chance that the IOP in the fellow eye would be within 2 mm, and a 78 to 95% chance that the IOP in the fellow eye would be within 3 mm.

## DIURNAL VARIATION OF IOP IN MEDICALLY TREATED PATIENTS WITH OPEN ANGLE GLAUCOMA

Different classes of anti glaucoma medication have been used in open angle glaucoma and their effects on the circadian intraocular pressure studied.

### **Prostaglandin analogues**

Prostaglandin analogues are one of the most efficacious topical antiglaucoma medications available now. They act primarily by increasing the uveoscleral outflow,

and to a lesser extent, the trabecular outflow. (64) They have been found to achieve mean IOP reductions of 24 to 29%, with bimatoprost and travoprost showing greatest efficacy.(51),(65) It has been shown that the peak IOP lowering effect of prostaglandins occurs 8 to 12 hours after administration.(67),(68) The once daily dosing of prostaglandin analogues makes it a convenient drug for patient use.

Latanoprost, a prostaglandin F2 alpha isopropyl ester prodrug, was the first commercially available drug in this class of antiglaucoma medication. Several studies have been performed to evaluate its efficacy. In a crossover trial by Orzalesi et al,(69) 10 patients with POAG and 10 with Ocular Hypertension (OHT) were treated with timolol, dorzolamide and latanoprost for one month each, in randomized sequence. A 24 hour IOP measurement was performed at baseline and after each month of treatment. It was found that all drugs reduced IOP significantly from baseline, except timolol at 3 am. It was found that latanoprost was more effective in lowering IOP than timolol and dorzolamide at most time points. Also, latanoprost seemed to lead to fairly consistent lowering of IOP throughout the circadian cycle.

A similar study was performed by Quaranta et al,(70) where 27 patients with newly diagnosed POAG were treated with timolol 0.5%, brimonidine 0.2%, dorzolamide 2%, and latanoprost 0.005% for 6 weeks each with 4 week washout periods between change of medication. 2 hourly intraocular pressure measurements were performed at baseline and at the end of each 6 weeks of medical treatment. It was found that latanoprost had a mean 24 hour IOP after treatment of  $16.62 \pm 0.98$  mm Hg, which was significantly lower than eyes treated with timolol ( $17.63 \pm 1.38$  mm Hg), brimonidine ( $18.32 \pm 1.50$  mm Hg), and dorzolamide ( $17.37 \pm 1.47$  mm

Hg). Although there was no significant difference in the IOP lowering efficacy of timolol and latanoprost during daytime hours, latanoprost was found to be more efficacious at each 2 hourly time point between 10 pm and 6 am. The authors concluded that although timolol was comparable to latanoprost in lowering daytime IOP, latanoprost brought about a uniform reduction in circadian IOP especially with regards to night time and early morning IOP.

The timing of administration of latanoprost is also thought to play a role in its IOP lowering efficacy. Alm et al(71) conducted a 6 month randomized multicenter trial with 267 patients. Out of these, 89 patients received a daily dosage of latanoprost 0.005% in the morning for 3 months, followed by in the evening for the next three months. 94 patients received the reverse schedule. Latanoprost applied in the morning was found to reduce the IOP from 25.5 to 17.7 mmHg (31%); and latanoprost applied in the evening, from 24.8 to 16.2 mmHg (35%). This difference was found to be statistically significant. It was concluded that latanoprost effected a greater reduction in IOP when administered in the evening.

In another study performed by Konstas et al(72), 33 patients with POAG were recruited and randomized to receive travoprost once a day, either in the morning or evening. After 8 weeks of treatment, a 24 hour IOP measurement was performed (4 hourly readings starting at 6 am). The groups were then switched and diurnal IOP recorded at the end of 8 weeks. It was found that there was no difference in the mean 24 hour IOP with morning or evening dosage of travoprost. However, evening dosed travoprost provided a better reduction of IOP at 10 am ( $17.2 \pm 2.1$  mmHg) than did the morning dosing ( $19.1 \pm 2.5$  mmHg). Moreover, evening dosing was found to have

a statistically lower 24-hour variation of IOP ( $3.2 \pm 1.0$  mmHg) than morning dosing ( $4.0 \pm 1.5$  mmHg), with similar safety in both groups.

The relative merits of different prostaglandin analogues have also been compared. Parrish et al(73) conducted a study to evaluate the daytime efficacy of latanoprost, bimatoprost and travoprost and compare all three. 410 patients with open angle glaucoma or ocular hypertension were included in this randomised double masked multicentre trial, held in 45 centres across the United States. At the end of 12 weeks of treatment, daytime IOP was found to be similar in all groups. Hyperemia was reported with lower frequency in the group treated with latanoprost.

Yildirim et al(74) conducted a randomised double masked trial in 48 patients with newly diagnosed primary open angle glaucoma. 15 patients were randomised to receive 0.05% latanoprost, 16 to receive 0.04% travoprost, and 17 to bimatoprost 0.03%, all as evening dosings. At the end of 8 weeks it was found that IOP levels were reduced 8.7 mm Hg at 8 am and 8.1 mm Hg at 10 am in patients treated with travoprost. Latanoprost-treated patients experienced 4.8 and 5.3 mm Hg reductions, whereas bimatoprost-treated patients experienced 5.5 and 4.9 mm Hg reductions at these time points. Travoprost was found to produce a significantly higher reduction in IOP at 8 and 10 am than did latanoprost and bimatoprost, but there was no significant difference at other time points.

However, in another multicentre randomized trial, Gandolfi et al(75) found contradicting results. 113 patients with POAG received bimatoprost and 119 received latanoprost (evening dosed) for 3 months. It was found that target IOP of less than 17 mm Hg was attained more frequently in the group treated with bimatoprost than with

latanoprost at the end of 3 months. Also, the mean 24 hour IOP was found to be about 1 mm lower in the group treated with bimatoprost.

DuBiner et al(76) found similar results as the above study. In 64 patients with POAG, latanoprost or bimatoprost were administered in the evening for 29 days. Bimatoprost was found to reduce the IOP by 5.9-8.9 mm Hg, i.e., a 25-34% reduction, whereas latanoprost was found to bring about a 20-31% reduction, i.e., 4.4-7.9 mm Hg. The difference was found to be statistically significant.

The study done by Seibold et al(77) in patients with POAG or OHT recorded daytime and night time IOP readings in patients treated with travoprost with the sofZia preservative. 24 hour IOP readings were performed at baseline, after 4 weeks of treatment and after discontinuation of the drug for 60 to 84 hours. It was found that the IOP was significantly lowered from baseline at each time point, and that the effects persisted throughout the 24 hour cycle even after 60 to 84 hours of discontinuation of the drug. However, in this study, travoprost lowered the IOP only by 16% in the daytime and 6% in the night time, with a mean 24 hour IOP lowering of 12%.

Another study performed by Konstas et al(78) compared the effects of preservative free tafluprost versus preservative containing latanoprost in 38 eyes with OHT or POAG with baseline pressures between 24 and 32 mm Hg. Tafluprost was found to demonstrate similar mean 24 hour efficacy of IOP reduction as compared to latanoprost (17.8 versus 17.7 mm Hg). Latanoprost demonstrated significantly lower 24 hour trough IOP (15.9 versus 16.3 mm Hg) whereas tafluprost was found to effect

a lower 24 hour IOP fluctuation (3.2 versus 3.8 mm Hg). There was no significant difference with respect to adverse effects among the two groups.

Bimatoprost is also available at a concentration of 0.01%. Tung et al(79) evaluated its efficacy in a study among 16 patients with POAG or OHT. Patients were housed in a sleep lab and underwent 2 hourly IOP measurements with a pneumotonometer in both sitting and supine positions during the 16 hour wake cycle, followed by 2 hourly supine measurements during 8 hours of the sleep cycle. They reported a 21.7% lowering of IOP during the day and 10.2% lowering during the night.

### **Topical Beta Blockers**

Timolol maleate is the most commonly used topical beta blocker. It acts by lowering the aqueous secretion. Timolol eyedrops are used in a concentration of 0.25% or 0.5%, as a twice daily dosage.

Konstas et al(80) evaluated the IOP lowering effect of Timolol 0.5% in 38 patients with POAG and 38 with pseudoexfoliation (PEX) glaucoma. It was found that the baseline IOPs were significantly higher at all time points with PEX glaucoma than in POAG in age matched patients. After treatment with timolol maleate, the reduction of the diurnal fluctuation of IOP was more pronounced in patients with PEX glaucoma(40%) than in patients with POAG (26%). Twenty-two (58%) of thirty eight patients with PEX glaucoma and twenty (53%) of thirty eight patients with POAG had peak IOP values outside office hours. Whereas twelve (32%) of the patients with POAG had IOP recordings of 18 mm Hg or less at all time points, only five (13%) of the patients with PEX glaucoma showed such IOP curves. The study concluded that

despite a greater initial IOP reduction in the patients with PEX glaucoma treated with timolol, this group still exhibited a higher IOP and significant fluctuation in the diurnal curve of IOP.

Orzalesi et al(69) in their crossover trial found that timolol was efficacious in lowering the daytime IOP, but had only half the IOP lowering effect at night (3 am). Quaranta et al(81) also reported that timolol was less efficacious during the night time, although its IOP lowering effect was comparable to that of latanoprost in the daytime. This observation has been attributed to the fact that beta blockers act by lowering aqueous secretion, which is physiologically lower at night time than during the day.

To overcome the drawback of twice daily dosing, timolol maleate has also been formulated in the gel form. This would allow for once daily dosing, freedom from preservatives and improved adherence. Shedden et al(82), in a randomized double masked multicentre trial, compared the efficacy of once daily dosing of timolol gel to a twice daily dosing of timolol solution. 286 patients with OAG were randomly assigned in a 2:1 ratio to the timolol gel group and the solution group. Diurnal IOP readings were measured at baseline, 2, 4, 8, 12 and 24 weeks. At the end of week 24, the mean reduction in IOP was found to be 5.6 to 5.9 mm Hg in the timolol gel group and 6.3 to 6.6 mm Hg in the timolol solution group. There was no significant difference in IOP among both groups with respect to the peak IOP. The timolol gel group, however, reported a more instances of blurring of vision and tearing than did the timolol solution group.

Quaranta et al(81) performed a similar masked crossover study in 28 patients with open angle glaucoma. Patients were treated with either 0.5% timolol solution or 0.1% timolol gel for 2 months, and then switched over to the other arm for 2 months. The investigators reported a reduction in the mean 24-hour IOP from  $23.1 \pm 0.7$  mm Hg at baseline to  $18.9 \pm 0.6$  mm Hg after timolol 0.5% and  $18.9 \pm 0.8$  mm Hg after timolol 0.1% hydrogel. Both formulations significantly decreased diurnal and nocturnal IOP, and the IOP at each time point, in a similar manner.

There has been only one study by Nielsen et al(83) comparing the effect of metoprolol 0.22 mg mounted on ophthalmic rods with timolol eye drops (0.5%). In this crossover study in 11 patients with open angle glaucoma, the authors reported similar diurnal efficacy in both these drugs. The mean IOP reduction was found to be 26% in both groups.

### **Topical Carbonic Anhydrase Inhibitors**

Carbonic anhydrase inhibitors bring about reduction in IOP by reducing the secretion of aqueous from the ciliary epithelium. The two commonly used medications in this class of drugs are dorzolamide hydrochloride 2% and brinzolamide hydrochloride 1%. Comparative studies between these two drugs have shown similar tolerability and efficacy in IOP lowering. In a study by Sall et al(84), in patients with PAOG and OHT, similar IOP lowering effects were found in three groups: IOP was lowered by 3.4 to 4.1 mm Hg (13.2% to 16.7%) with brinzolamide 1.0% administered twice a day; by 4.1 to 4.8 mm Hg (16.6% to 19.1%) with brinzolamide 1% administered thrice a day; and by 4.3 to 4.9 mm Hg (16.9% to 20.1%) with



dorzolamide 2.0% instilled thrice a day. Other studies have also found that dorzolamide monotherapy with a thrice daily dosage reduces the mean diurnal IOP by 16 to 26%.<sup>(85), (86)</sup>

Contrary to beta blockers (which also lower IOP by reducing aqueous secretion), carbonic anhydrase inhibitors have been found to have a better IOP lowering action at night time. The decreased nocturnal efficacy of beta blockers may be explained by the physiologically lower levels of circulating catecholamines during the night.<sup>(87)</sup> Orzalesi et al's study<sup>(88)</sup> found that dorzolamide 2% in a thrice daily dosage was more effective at lowering IOP at midnight and 3 am than timolol 0.5%, although the latter showed a better IOP reduction in the evening hours. They also reported no statistically significant difference between the mean 24 hour IOPs among the two groups.

A randomized multicentre trial by Strahlman et al<sup>(89)</sup> compared the IOP lowering efficacy of dorzolamide 2% as a thrice daily dosage with that of 0.5% timolol maleate and 0.5% betaxolol hydrochloride, each administered twice daily. 523 patients with POAG or OHT were recruited and followed up for one year. At the end of one year, the mean percent reduction in intraocular pressure at the daytime peak in 2% dorzolamide, 0.5% timolol, and 0.5% betaxolol was approximately 23%, 25%, and 21%, respectively. At afternoon trough, the mean percent reduction in intraocular pressure was 17%, 20%, and 15% for dorzolamide, timolol, and betaxolol, respectively. This study, however, did not record night time IOPs.

Stewart et al(51) in their meta analysis of 24 hour efficacy of glaucoma medication, found that topical carbonic anhydrase inhibitors had a better night time than daytime efficacy. IOP was found to be reduced by an average of 16% during the daytime, and 21% during the night time, by a thrice daily dosage of dorzolamide.

### **Alpha Adrenergic Agonists**

Brimonidine is a highly selective alpha 2 agonist which may be administered in a twice daily or thrice daily regimen. Stewart et al(90) in a study on 40 patients with POAG, found a mean reduction in IOP of 14 to 19% with brimonidine 0.2% administered thrice a day. Other studies(51), (91) found similar results.

Brimonidine, however, has been found to have decreased efficacy in lowering the night time IOP. Liu et al(92) in a study on 15 patients with OAG housed in a sleep laboratory, found that though brimonidine 0.2% in a twice daily dose led to a significant reduction in the daytime IOP by 12.5%, there was almost no reduction in the night time IOP. Orzalesi et al(88) reported similar findings, with minimal efficacy of brimonidine at 3 am and 6 am.

Konstas et al(93) in a crossover double blind trial, evaluated the 24 hour efficacy of brimonidine 0.2% administered twice, or three times daily versus timolol maleate 0.5% given twice daily in patients with POAG. The mean 24 hour IOP for brimonidine twice daily and three times daily was 19.2 mmHg and 18.0 mmHg, respectively, whereas for timolol it was 17.7 mmHg. There was a statistically significant difference among all three groups. Moreover, pair-wise comparisons

showed that thrice daily brimonidine or twice daily timolol reduced IOP more than twice daily brimonidine at every time point after 10:00 am. In contrast, thrice daily brimonidine and twice daily timolol were statistically similar over the 24 hour period, except at 4:00 pm when timolol maleate performed significantly better. This group of investigators also reported that three-times-daily brimonidine provided significantly better late afternoon and early night time efficacy than twice-daily dosing.

### **Fixed combination therapies and their 24 hour efficacy**

Most patients with glaucoma need more than one topical medication to reach the pre determined target IOP. According to the Lichter et al in the Collaborative Initial Treatment of Glaucoma Study (CIGTS)(94), 75% of patients with open angle glaucoma need 2 or more medications to reach target IOP. Fixed dose combinations, as compared to concomitantly administered antiglaucoma medication, have the advantage of ease of administration, better compliance, and less exposure to preservative. However, there are few studies comparing the efficacy of these two groups.

### **Combination of Carbonic Anhydrase Inhibitors with Beta Blockers**

Stewart et al(51) in their meta analysis of clinical trials on the diurnal IOP reduction with anti glaucoma medication, reported a mean IOP lowering efficacy of 26% for a fixed dose combination of dorzolamide and timolol.

In another randomized double masked multicentre trial by Feldman et al(95), 230 patients with POAG or OHT were randomized to receive either a dorzolamide

2%/timolol 0.5% fixed dose combination (DTFC) twice a day, or timolol 0.5% twice a day. At the end of 8 weeks, the investigators reported a significant reduction in day time and night time IOP at all 8 time points in both groups; but the reduction with DTFC was significantly higher.

Eren et al(96) compared the effect of dorzolamide 2%/timolol 0.5% fixed dose combination (DTFC) twice a day, with that of latanoprost 0.005%/timolol maleate 0.5% fixed combination (LTFC) once a day on diurnal intraocular pressure (IOP) in 33 patients with primary open-angle glaucoma. Patients were treated with each drug combination for 6 weeks, followed by a 6 week washout period and a crossover to the other arm. Diurnal 4 hourly IOP readings were performed at baseline and at the end of each 6 week period. Mean baseline IOP was 25.1 mm Hg. The investigators found a mean post treatment IOP of 16.3 mmHg with LTFC and 17.3 mmHg with DTFC. This difference was statistically significant.

Konstas et al(97) performed a 6 week crossover study to compare the 24 hour efficacy of latanoprost 0.005% versus DTFC. The mean 24 hour IOP for the DTFC group was  $15.3 \pm 2.0$  mm Hg, and for the Latanoprost group was  $15.9 \pm 2.3$  mm Hg. There was no significant difference in the mean IOPs among the two groups at any time point except at 10m, when the latanoprost group had an IOP of  $16.6 \pm 3.1$  mm Hg and the DTFC group had an IOP of  $14.6 \pm 2.7$  mm Hg.

## **Combination of Prostaglandin Analogues with Beta Blockers**

Latanoprost 0.005% and timolol 0.5% fixed combination (LTFC) administered once a day was found to have a mean 24 hour IOP lowering efficacy of 33%.(51) In a 2 month crossover trial by Konstas et al(98), 34 patients with POAG were treated with timolol 0.5% twice a day, and LTFC as an evening dose. The diurnal IOP curves showed that LTFC was more efficacious than timolol at all time points. The mean baseline IOP was 25 mm Hg. After treatment with timolol, the 24 hour IOP mean was 19.3 mm Hg, whereas after treatment with LTFC, the 24 hour mean was 16.4 mm Hg, the difference between which was statistically significant. Similar results were obtained in a later trial.(99)

The efficacy of timolol 0.5% and travoprost 0.04% fixed combination (TTFC) was evaluated in a 4 month crossover study by Konstas et al(100). This study compared the effects of evening versus morning administration of once daily TTFC in 32 patients with either POAG or PEX glaucoma. Mean baseline 24 hour IOP was 27.7 mmHg and both groups showed a highly significant IOP reduction at all time points. The authors reported that compared to morning dosing, the evening dosing of TTFC recorded significantly lower mean 24 hour IOP (18.4 versus. 19.2 mmHg) and significantly reduced 24 hour fluctuation (3.8 versus. 5.1 mmHg).

## **Combination of Carbonic Anhydrase Inhibitor with Timolol**

Tamer et al(100) in a randomized crossover trial in 36 patients with POAG treated with latanoprost monotherapy with resulting uncontrolled intraocular

pressures, found an additional ocular hypotensive effect of 3.2 mmHg over 24 h when dorzolamide was added to latanoprost. Timolol was less effective over 24 h when added to latanoprost (2.6 mmHg). Importantly, when all time points were analyzed in this trial, dorzolamide was superior to timolol in five out of the eight time points evaluated.

Naksamura et al(101) in their randomised crossover trial in 20 patients received a combination of latanoprost with either dorzolamide or brinzolamide. Both groups showed a significant reduction in IOP from baseline, and there was no statistically significant difference in reduction among the two groups.

#### DIURNAL VARIATION OF IOP IN SURGICALLY TREATED PATIENTS

Surgery has been considered the mainstay of therapy, especially in advanced glaucomas. Although Laser trabeculoplasty is also a treatment modality for open angle glaucoma, with some studies showing that it is efficacious in reduction of IOP throughout the 24 hour period(102), (103), there are few studies proving the long term efficacy of this procedure. Also, 3 to 5 % of treated eyes may show a rise in IOP.(104)

Trabeculectomy has been found to be an efficacious and safe method of IOP lowering in most types of open angle glaucoma. It has been found to lower IOP to safe and acceptable levels and also provide long term IOP control. A study by Saiz et al(105) in 26 eyes of 14 patients with open angle glaucoma compared diurnal IOP curves prior to treatment, one year after trabeculectomy and 5 years after trabeculectomy. They reported a significantly lower IOP from baseline even at 5 years, with a daytime diurnal range of  $4.8 \pm 2.5$  mm Hg.



Gandolfi et al(106) in a prospective randomized control trial in 24 patients with glaucoma and cataract, evaluated the effectiveness of trabeculectomy with 5 fluorouracil versus trabeculectomy without the antimetabolite adjunct. At the end of a 1 year follow up, 2 hourly daytime IOP was measured from 8 am to 6 pm. It was found that 10 of 12 eyes of the 5-FU group recorded a mean IOP of 15 mmHg or less at the end of 1 year as opposed to 1 of 12 eyes in the group without 5-FU. The IOP fluctuation was 10 to 17 mmHg in the 5-FU group and 14 to 22 mmHg in the control group.

Klink et al(107) compared diurnal and nocturnal IOP fluctuations before and after trabeculectomy in 35 patients with POAG. The pre operative peak IOP was found to be  $26.5 \pm 5.9$  mm Hg in the daytime and  $23.4 \pm 5.2$  mm Hg at night time. At a followup after at least 300 days, the postoperative diurnal and nocturnal IOP peaks were  $16 \pm 4.4$  and  $16 \pm 5.4$  mm Hg, respectively. Pre- to postoperative IOP reductions were statistically different (day 40% and night 32%;). Diurnal fluctuation was reduced significantly from  $12.1 \pm 4.2$  mm Hg preoperatively to  $5.6 \pm 2.2$  mm Hg postoperatively (reduction of 54%), and nocturnal fluctuation from  $7.1 \pm 4.5$  to  $3.9 \pm 4.1$  mm Hg (reduction of 46%), respectively.

In a similar study, Ross et al(22) analyzed the Diurnal IOP profiles in patients with open angle glaucoma, pre and post trabeculectomy, compared to a group of medically controlled patients. Fifteen eyes post trabeculectomy surgery served as the study group whereas a group containing 17 eyes controlled on topical antiglaucoma medication served as the control group. There was a statistically significant reduction in both mean IOP of 3.7 mmHg and peak IOP of 4.4 mmHg in the surgical group

compared to the medical group. There was no statistically significant change in the IOP fluctuation between the 2 study groups .

There are very few studies comparing the efficacy of surgical treatment versus medical treatment with regard to the circadian variation of IOP. Medeiros et al(108) in their study on IOP fluctuations during daytime hours, compared a group of 30 patients with POAG on antiglaucoma medication, with 30 eyes subjected to one or more trabeculectomies. All subjects were submitted to a day diurnal measurement of IOP from 8:10 am till 5 pm for every three hours, followed by the water drinking test. Although the mean post treatment IOP was similar among the two groups, the IOP fluctuation were significantly higher in the medical group ( $3.2 \pm 1.5$  mm Hg) than in the surgical group ( $2.2 \pm 1.7$  mm Hg). The peak IOP was also lower in the surgical group. A similar effect was seen following the water drinking test. From an overall baseline IOP of 10.6 mmHg, the mean IOP change following the WDT was 13% in the surgical group and 40% in the medical group.

Mansouri et al(109) compared the effect of latanoprost 0.05% versus trabeculectomy and deep sclerectomy in 60 prospectively recruited subjects with primary open-angle glaucoma. The medical group comprised 20 patients with controlled IOP ( $<18$  mm Hg) with latanoprost 0.005% monotherapy and with no previous intraocular surgery or argon laser trabeculoplasty; the surgical groups included 20 patients after trabeculectomy, and 20 patients after deep sclerectomy with collagen implant (DSCI). They performed daytime IOP measurements and also IOP measurement after a water drinking test. The mean IOP was found to be lower in the trabeculectomy group (10.1 mm Hg) as compared to the DCSI group (13.7 mm Hg)

and the medical group (15.7 mm Hg). However, the IOP fluctuations were comparable among the three groups. Also, the medical group showed a higher elevation of IOP after the water drinking test (5.2 mm Hg) than did the DSCI group (3.8 mm Hg) and the trabeculectomy group (2.4 mm Hg).

Konstas et al(20) compared the 24 hour IOP curves in patients with advanced glaucoma, with seemingly controlled intraocular pressures after having undergone trabeculectomy with those who were controlled with maximal medical management. In this prospective trial conducted in a tertiary eye care centre in Greece, 60 patients above the age of 39, who had been diagnosed with either POAG or PEX glaucoma, and whose eye had been classified according to the advanced Glaucoma Intervention Study Visual Field classification score of 11 or more (moderate to severe damage) were enrolled. Patients in the medical group were phakic patients who had a controlled IOP (18 mm Hg or less during office hour visits) with 2 to 4 topical antiglaucoma medication of any class. Patients in the surgical group were phakic or pseudophakic patients who had undergone trabeculectomy with or without cataract surgery at least 6 months prior to recruitment. A well functioning bleb, the absence of any adjunctive antiglaucoma medication and absence of any other prior surgical or laser procedures were also pre requisites for recruitment.

Patients in both groups were matched at the recruitment visit into pairs, based on an IOP within 1 mm Hg of each other at 10 am or within 1 hour. They were then hospitalized at the next visit to undergo diurnal IOP measurements using Goldmann Applanation Tonometry by the investigators at 6 time points- 10am, 2 pm, 6 pm, 10 pm, 2 am and 6 am. The IOP curves were then compared.

It was found that a statistically lower mean IOP was observed in the surgical group ( $12.1 \pm 2.2$  mm Hg) as compared to that in the medical group ( $13.5 \pm 2.0$  mm Hg). The surgical group also exhibited a significantly lower IOP at each time point except 10am. The diurnal range (fluctuation) of IOP and the peak IOP were significantly lower in the surgical group. ( During the IOP monitoring, no patients in the surgical group, and 11 patients in the medical group had an IOP of more than 18 mm Hg at some time point. The study concluded that in spite of seemingly well controlled IOP in medically managed patients with advanced glaucoma, undetected fluctuations with peaks pose a risk for progression of glaucoma.

A study by Matsuoka et al(110) in 14 eyes of 8 open angle glaucoma patients who had undergone combined trabeculotomy with sinusotomy, compared the pre and post operative intraocular pressure profiles. It was found that the post operative diurnal IOP curves showed a blunting of fluctuations, with significant reductions in the mean postoperative mean IOP ( $16.5 \pm 1.7$  to  $13.9 \pm 2.0$  mm Hg) and the peak IOP ( $21.9 \pm 2.4$  to  $16.1 \pm 2.5$  mm Hg).

In spite of significant differences in the diurnal IOP profiles between surgically and medically managed patients, very few such studies comparing the two groups have been undertaken. Specifically, in India, no such studies have been published. Hence this study was undertaken with the aim of comparing the effects of medical management versus surgical treatment on the control of IOP over a 24 hour period.

## MATERIALS AND METHODS

This was a prospective observational study conducted at the Department of Ophthalmology, Christian Medical College, Vellore. The study aimed to compare the peak intraocular pressure lowering effects as well as diurnal fluctuations of intraocular pressure in patients who have attained target intraocular pressure following trabeculectomy or by ocular hypotensive medications.

Patients who visited the General Outpatient Department (OPD) or the Glaucoma Clinic at the Department of Ophthalmology, Christian Medical College, Vellore who fulfilled the eligibility criteria were included in the study after informed consent. The two groups of patients included those with diagnosed open angle glaucoma, who had undergone trabeculectomy (isolated trabeculectomy or trabeculectomy with cataract surgery) and those on topical ocular hypotensive medication, who had attained 30% reduction from the original baseline IOP. This was determined from the office hour intraocular pressure measurements that were performed in the Outpatient department during routine follow up after the surgery or initiation of medical management.

A questionnaire was administered to all participants of the study. Each participant was hospitalized for a 24 hour period as part of the study and underwent measurement of intraocular pressure (IOP) by the principal investigator over a 24- hour period at four hour intervals( 6 am, 10 am, 2 pm, 6 pm, 10 pm and 2 am ). The IOP was measured with a Goldmann Applanation Tonometry (GAT) and with a Tonopen XL (Reichert, Inc.) in sitting position at 10 am, 2 pm, 6 pm and 10 pm and in supine position with Tonopen and sitting position with GAT at 2:00 am and 6:00 am. Diurnal tension curves were plotted for each eye

and the collated data analysed. The peak IOP, mean IOP and range of diurnal variation of IOP between the two groups were compared.

The eligibility criteria for the study were as follows:

- Above the age of 18
- Diagnosed with open angle glaucoma
- Should have undergone filtering surgery (trabeculotomy) or should have been started on ocular hypotensive medication at least three months prior to recruitment
- Should be “controlled”, i.e., office measurement of intraocular pressure should be 30% from the initial baseline IOP prior to medical or surgical therapy

Exclusion criteria included:

- Patients unwilling to give informed consent/ unable to come for follow up visits
- Patients with Normal Tension Glaucoma (NTG) defined as patients with baseline IOP  $\leq 21$  mmHg with characteristic disc and field changes of open angle glaucoma
- Pigmentary glaucoma
- Patients who have undergone laser peripheral iridotomy
- Patients who have been on steroid eye drops in the past three months
- Pregnant or lactating women
- Patients on systemic carbonic anhydride inhibitors



- Patients who have undergone any ocular surgery besides uneventful cataract surgery and/or trabeculectomy
- Patients with history of significant ocular trauma at any time
- Patients with active ocular infection or inflammation
- Patients who have not attained target intraocular pressure

The primary outcome of the study was the comparison of the diurnal intraocular pressure profiles in patients with open angle glaucoma who had undergone trabeculectomy or were on topical ocular hypotensive medication, who are controlled as per office IOP measurements.

Target IOP was defined as the intraocular pressure at which the clinician expects the ganglion cell death to be no greater than the age dependent rate, or the highest IOP at which no clinically apparent optic nerve damage occurs. It has varying definitions:

- The collaborative normal tension glaucoma study (CNTGS) found that lowering of the IOP by 30% from the baseline was effective in slowing disease progression(111)
- Many authors recommend maintaining an IOP range in the early teens, especially in advanced glaucomas(57)

The various parameters considered in each diurnal curve were as follows:

- The peak IOP was defined as the highest IOP recorded during a diurnal measurement,
- The trough IOP was defined as the lowest IOP recorded during a diurnal measurement.

- The mean IOP was defined as The arithmetic mean of all IOPs recorded over the 24 hour period.
- The diurnal fluctuation of IOP was defined as the difference between the peak and trough IOPs recorded during a diurnal measurement.

Potential confounders in the study included age, gender, exercise, hypertension, systemic medication such as prostaglandins and vasodilators.

Data regarding inclusion and exclusion criteria were obtained by a detailed history and clinical examination of the patients. Data regarding confounding factors were also obtained by a detailed questionnaire.

Intraocular pressure was measured by Goldmann applanation tonometry using a Haag Streit slit lamp, which is the gold standard for IOP measurement, and additionally with a Tonopen XL in supine position at 2 am and 6 am. Measurements were done by the principal investigator.

For the sample size calculation, the study “24 hour IOP Control with Maximum Medical Therapy compared with Surgery in Advanced Open Angle Glaucoma” by Konstas et al was used. The average maximum IOP for the surgical group was  $13.4 \pm 2.3$  mm Hg and medically treated patient group was  $16.3 \pm 4$  mm Hg according to this study. The sample size is calculated using nMaster software version 2.0.

## Two Means - Hypothesis testing for two means

Standard deviation in group I	2.3
Standard deviation in group II	4
Mean difference	4
Effect size	1.27
Alpha error (%)	5
Power (1- beta) %	80
1 or 2 sided	2
Required sample size per group	10

### Formula

$$n = \frac{2s_p^2 [z_{1-\alpha/2} + z_{1-\beta}]^2}{\mu_d^2}$$

$$s_p^2 = \frac{s_1^2 + s_2^2}{2}$$

Where,

$s_1^2$  : Standard deviation in the first group

$s_2^2$  : Standard deviation in the second group

$\mu_d^2$  : Mean difference between the samples

$\alpha$  : Significance level

$1-\beta$  : Power

With the mean difference of 4, alpha error of 5%, power 80% with the two sided test, the study required totally 20 patients in each arm, that is, a total of 40 patients. To prove the efficacy of surgery over medical management in lowering the peak IOP in open angle glaucoma, the study required a total of 40 patients.

For continuous data such as age, the descriptive statistics n, Mean, SD, Median, IQR, Minimum and Maximum were calculated. For categorical data, the number of patients and percentage were calculated. The average IOP was calculated for each time point for both groups, and plotted to see the trend of diurnal variation. The mean and peak IOPs in the two groups were compared. The diurnal range or fluctuation of IOP was calculated for each patient and compared among the two groups.

The parametric t test was applied to see the mean difference between two groups (medically treated and surgical groups). The Chi-square test was applied to the data.

P-values were reported as specified by the statistical software used, at least up to three decimal places. P-values less than 0.0001 were reported as provided by statistical software (e.g. '<0.0001'). All tests were two-sided at  $\alpha=0.05$  level of significance. All statistical analysis were done using SPSS software version 17.0.

## RESULTS

### Demographic characteristics

40 eyes of 22 patients were recruited for this study, 20 in the medical arm and 20 in the surgical arm. The medical group had 11 male and 9 female patients, whereas the surgical group had 7 male and 13 female patients. Both eyes were recruited in 19 patients.

**Table 1: Table showing the gender distribution of patients in the two groups**

	Medical group	Surgical group
Male	11	7
Female	9	13
Total	20	20

### Co- morbidities in participants

**Hypertension:** 9 out of 22 patients recruited were hypertensive. 2 out of the 9 were on beta blockers whereas the rest were on treatment with calcium channel blockers. The medically treated group had more hypertensive patients than did the surgical group.

**Diabetes Mellitus:** 8 patients recruited were diabetic, on oral hypoglycaemic agents. 16 of the eyes studied belonged to diabetic patients, out of which 10 were in the medical group and 6 in the surgical group. None of the recruited patients had any diabetic retinopathy.

### **Baseline characteristics**

40 eyes with Primary Open Angle Glaucoma (POAG) or Pseudoexfoliation glaucoma (PEX Glaucoma) were included in this study. Both surgical and medical groups had 18 eyes with POAG and 2 eyes with PEX Glaucoma.

**Table 2: Table showing the type of glaucoma in the recruited patients in the two groups**

	Medical Group	Surgical group
POAG	18	18
PEX glaucoma	2	2
Total	20	20



### **Details of anti-glaucoma medications in the medical group**

Among the eyes in the medical group, 6 patients were on a single ocular hypotensive medication whereas 14 were on combination therapy. The different drugs used were as given in the table below:

**Table 3: Table showing the number of patients on each combination of anti glaucoma medication**

<b>Anti-glaucoma Medication</b>	<b>Number Of patients</b>
Only Beta blocker	2
Only prostaglandin analogue	4
CA Inhibitor + Beta blocker	6
CA Inhibitor + Beta blocker + PG Analogue	6
CA Inhibitor + Beta blocker + PG Analogue + Alpha Agonist	2
<b>Total</b>	<b>20</b>

**Baseline IOP characteristics:**

In both the medical and surgical groups, eyes in which 30% reduction or more from baseline IOP (IOP prior to treatment) had been achieved as noted from office hour IOP measurements (performed in the outpatient department) were recruited into the study. The pre treatment office hour IOP data was obtained from the previous outpatient chart documentation of the patients. The pre treatment and post treatment characteristics of IOP in the two groups are as given below. (Tables 4 and 5)

**Table 4: Table showing pre-treatment and post-treatment IOP in the two groups**

	Medical group	Surgical group	P value
Mean Pre treatment baseline IOP (mm Hg)	27.00 $\pm$ 4.63	32.00 $\pm$ 4.94	0.773
Mean Post treatment office hour IOP (mm Hg) GAT	15.10 $\pm$ 3.16	15.40 $\pm$ 3.10	0.989

**Table 5: Table showing reduction in IOP among the two groups**

	Medical group	Surgical group	P value
Mean reduction in IOP (mm Hg)	$11.9 \pm 3.00$	$16.6 \pm 4.48$	0.647
% reduction in IOP	$43.99 \pm 7\%$	$51.49 \pm 9\%$	0.880

There was no significant difference in the pre or post treatment baseline characteristics among the two groups of eyes.

### Comparison of GAT and Tonopen intraocular pressures in the two groups:

Table 6 shows the details of GAT and Tonopen IOP measurements at each time point.

**Table 6: Table showing Mean IOP as measured by GAT and Tonopen at each time point, in the two groups**

	Med GAT (mm Hg)	Med Tono (mm Hg)	P value	Surg GAT (mm Hg)	Surg Tono (mm Hg)	P value
10 am	15.25 ± 3.46	13.35 ± 4.15	0.940	12.45 ± 2.41	12.25 ± 3.11	0.995
2 pm	15.35 ± 2.30	14.15 ± 3.06	0.860	12.70 ± 2.38	12.15 ± 1.67	0.970
6 pm	14.7 ± 2.65	13.75 ± 2.98	0.460	12.65 ± 2.32	11.55 ± 2.43	0.985
10 pm	14.8 ± 2.11	13.2 ± 2.21	0.851	12.95 ± 3.42	11.85 ± 3.00	0.896
2 am	15.85 ± 3.73	14.35 ± 3.54	0.761	12.8 ± 2.96	11.95 ± 2.93	0.914
6 am	16.5 ± 3.33	14.8 ± 3.34	0.362	12.6 ± 3.32	12.25 ± 3.46	0.970

Med – Medical group; Surg – Surgical group; GAT – Goldmann Applanation Tonometry Tono- Tonopen

There was no statistically significant difference in the IOP as measured by Tonopen and GAT.

**Mean, peak and trough of the 24 hour IOPs among the two groups:**

Table 7 shows the mean, peak and trough of the 24 hour intraocular pressures in the two groups

**Table 7: Table showing the peak and trough of the 24 hour IOPs among the two groups**

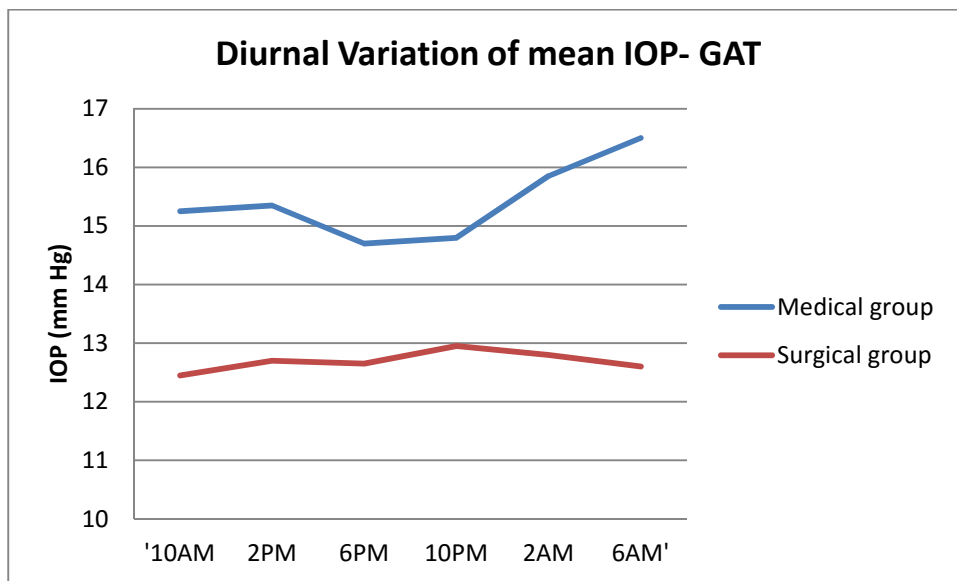
	Medical group	Surgical group	P value
Mean pre recruitment IOP (mm Hg)	15.10 $\pm$ 3.16	15.40 $\pm$ 3.10	0.989
Mean 24 hour IOP (mm Hg)	15.40 $\pm$ 1.95	12.67 $\pm$ 2.30	0.171
Peak IOP (mm Hg)	18.65 $\pm$ 2.39	15.05 $\pm$ 2.98	0.237
Trough IOP (mm Hg)	12.6 $\pm$ 1.93	10.5 $\pm$ 1.79	0.182

In the medically managed group, the peak IOP in the 24 hour period was found to be higher than in the surgically managed group. The mean IOPs also showed a similar trend, being lower in the surgical group, though these differences were not statistically significant.

### Diurnal IOP (24 hour phasing) Curves

The diurnal IOP variation at each time point were plotted with the patient in seated position for both groups as measured by GAT (Figure 1)

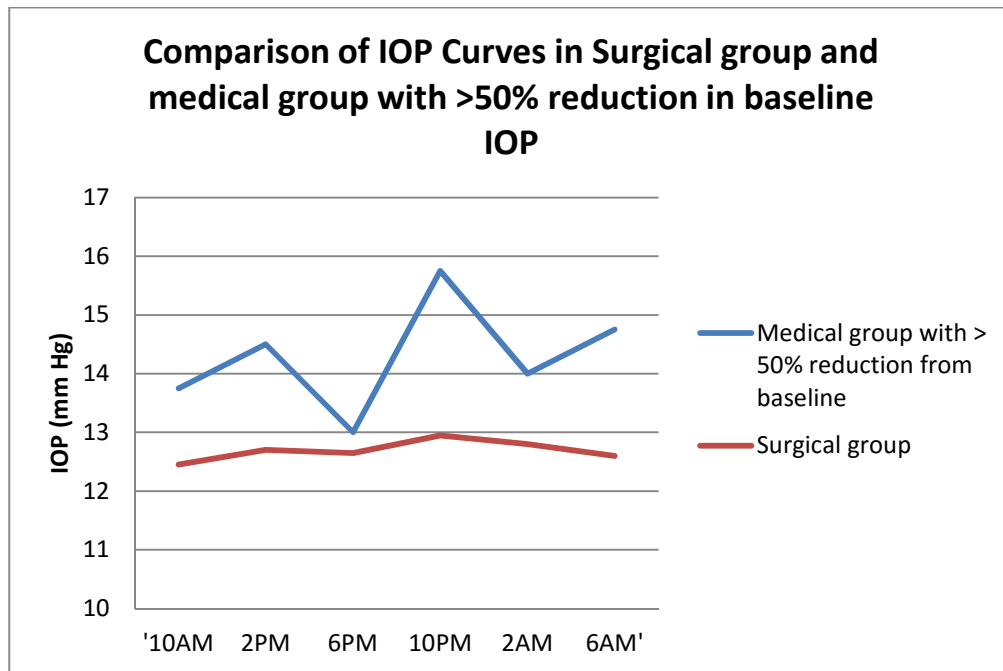
**Figure 1: Plot showing the diurnal variation of mean intraocular pressure at each time point as measured by Goldmann Applanation Tonometry (in seated posture) in the medical group and the surgical group**



The medical group showed a peak in the early morning 6am recordings. The peak IOP was within 2 mmHg of the trough seen late evening. The surgical group showed almost similar IOP throughout the 24 hour phasing with no peaks or troughs. However the IOP in the surgical group was at all times lower than in the medical group.

The mean IOP reduction in the surgical group was  $43.99 \pm 7\%$  as compared to  $51.49 \pm 9\%$  in the medical group. Hence we looked among those patients in the medical group, who achieved a reduction in IOP comparable to the surgical group ( $>50\%$ ). There were 4 such eyes and their diurnal variation curves were analysed and compared to the surgical group (Figure 2 ).

**Figure 2: Graph showing the 24 hour intraocular pressure curves in the surgical group and those eyes in the medical group which had more than 50% reduction from baseline (GAT IOP measurements)**



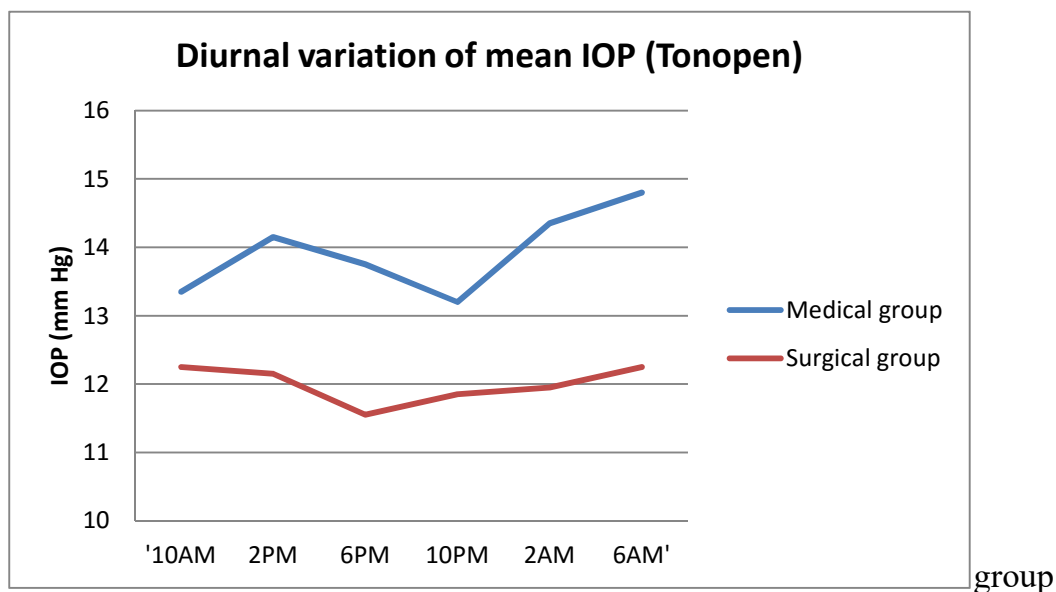
The medical group still showed variation in IOP as compared to the surgical group. However their numbers were too small to make statistically significant conclusions.

## Variation in IOP with posture

### Effect of posture on the diurnal (24 hour phasing) variation of IOP:

IOP was recorded in supine position at the patient's bedside at 2am and 6am using Tonopen. To avoid inter device differences, the daytime IOP measurements with Tonopen were considered for comparison and not the GAT measurements. The plotting of IOP with Tonopen at each time point is shown in Figure 3.

**Figure 3: Plot showing the diurnal variation of mean intraocular pressure at each time point as measured by Tonopen in the seated posture at 10 am, 2 pm, 6 pm and 10 pm, and in the supine posture at 2 am and 6 am, in the medical group and the surgical**



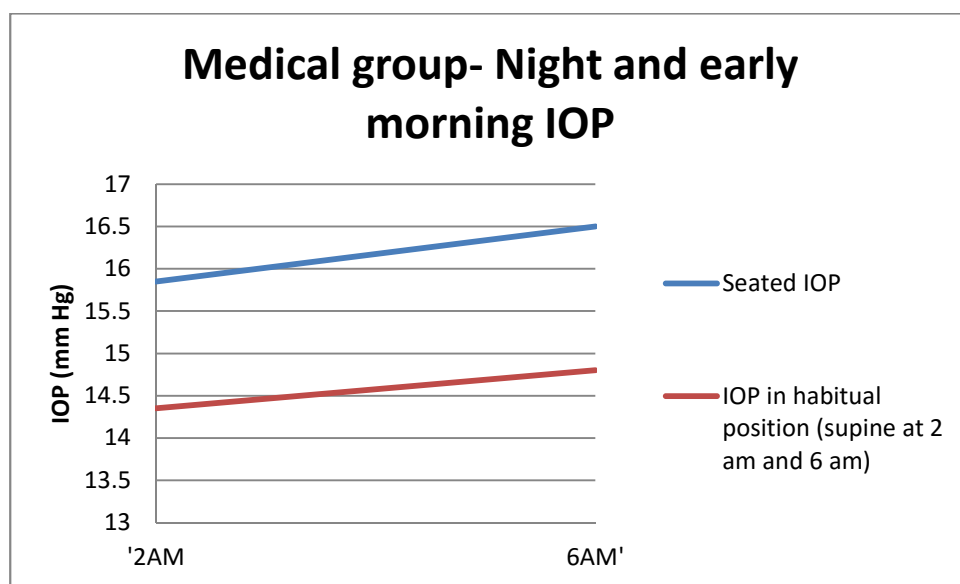
The medical group showed a peak in the early morning and a trough late evening. A small peak was noted at 2pm. The surgical group showed minimal variation through the 24 hours.



### Comparison of the supine tonopen IOP and seated GAT IOP at 2am and 6am:

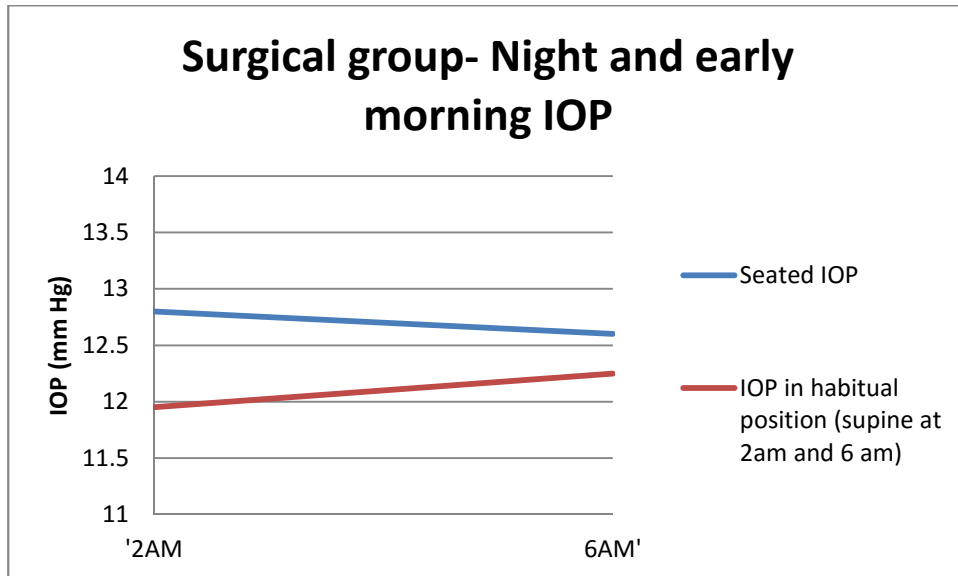
The Tonopen measurements were taken at 2am and 6am in the supine position at the bedside followed by GAT IOP in the seated position 5 minutes later. The details in the medical group are shown in Figure 4 and in the surgical group in Figure 5.

**Figure 4: Plot showing the night time and early morning variation of mean intraocular pressure as measured by GAT in the seated posture and with Tonopen in the supine posture at 2 am and 6 am, in the medical group**



In the medical group (Figure 4), the plotting of the IOP in the seated position (GAT) and supine position (Tonopen) at 2am and 6am showed similar pattern with the GAT seated IOP being slightly higher than the supine Tonopen IOP. This could be explained by the inter device difference rather than the posture. As noted at the beginning (table 6) GAT tended to measure the IOP slightly higher than the Tonopen. Hence short term change in posture – seated GAT being measured 5 minutes after the supine Tonopen IOP did not seem to affect the IOP.

**Figure 5: Plot showing the night time and early morning variation of mean intraocular pressure as measured by GAT in the seated posture and with Tonopen in the supine posture at 2 am and 6 am, in the surgical group**



In the surgical group (Fig 5) both the supine tonopen IOP and seated GAT IOP were almost similar.

### **Comparison of the fluctuation of 24 hour IOP among the two groups:**

Details of the fluctuation of IOP over 24 hours in the two groups are shown in Table 8.

**Table 8: Table showing the mean intraocular pressures and the mean fluctuation of intraocular pressure in the two groups over a 24 hour period (GAT readings)**

	Medical group	Surgical group	P value
Mean 24 hour IOP (mm Hg)	15.40 $\pm$ 1.95	12.69 $\pm$ 2.30	0.171
Mean fluctuation 24 hour variation (mmHg)	6 $\pm$ 1.97	4.25 $\pm$ 1.91	0.129

Though there was no statistically significant difference in the mean 24 hour IOP or the amount of variation in the IOP in the two groups, the mean IOP as well as the variation in IOP was lower in the surgical group as compared to the medical group

**Comparison of the fluctuation of IOP in the two groups during office hours:**

Table 9 shows the details of the fluctuation of IOP in the two groups during office hours.

**Table 9: Table showing the mean intraocular pressures and the mean fluctuation of intraocular pressure in the two groups over office hours (10am, 2 pm and 6 pm)**

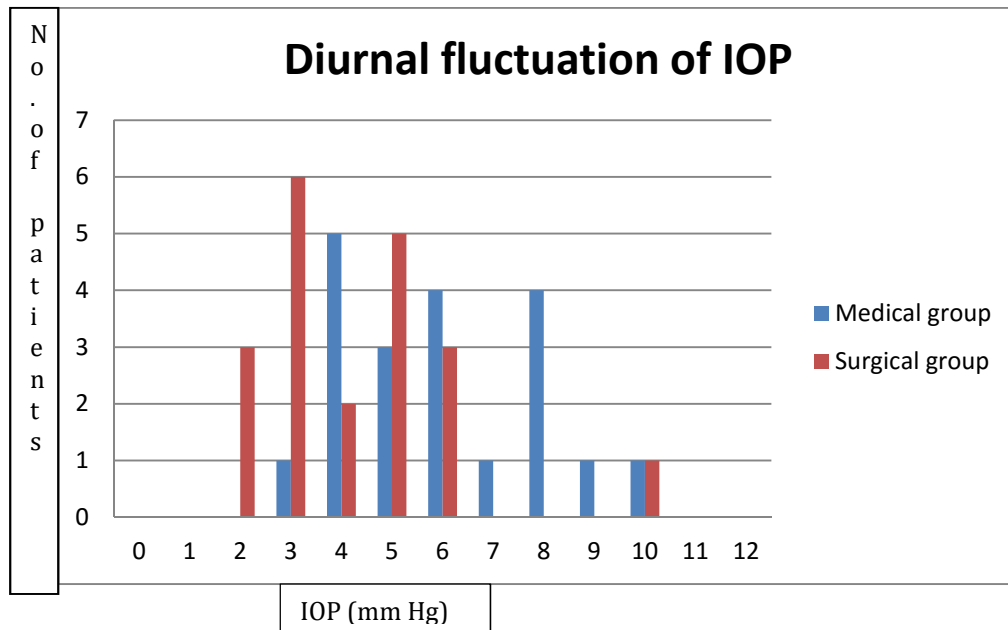
	Medical group	Surgical group	P value
Mean office hour IOP (mm Hg)	15.10 $\pm$ 2.21	12.6 $\pm$ 1.86	0.171
Mean office hour fluctuation of IOP	3.33 $\pm$ 2.08	2.95 $\pm$ 1.60	0.488

There was no statistically significant difference when the office hour IOPs (measured at 10 am, 2 pm and 6 pm) were considered. However the surgical group trended to have lower IOP as well as lesser fluctuation as compared to the medical group.

### Fluctuation of IOP during 24 hours in individual patients in the two groups:

Figure 6 shows the details of the amount of fluctuation of IOP during 24 hours in the individual patients in the two groups

**Figure 6: Graph showing the 24 hour fluctuation of intraocular pressure in the medical and medical and surgical groups**



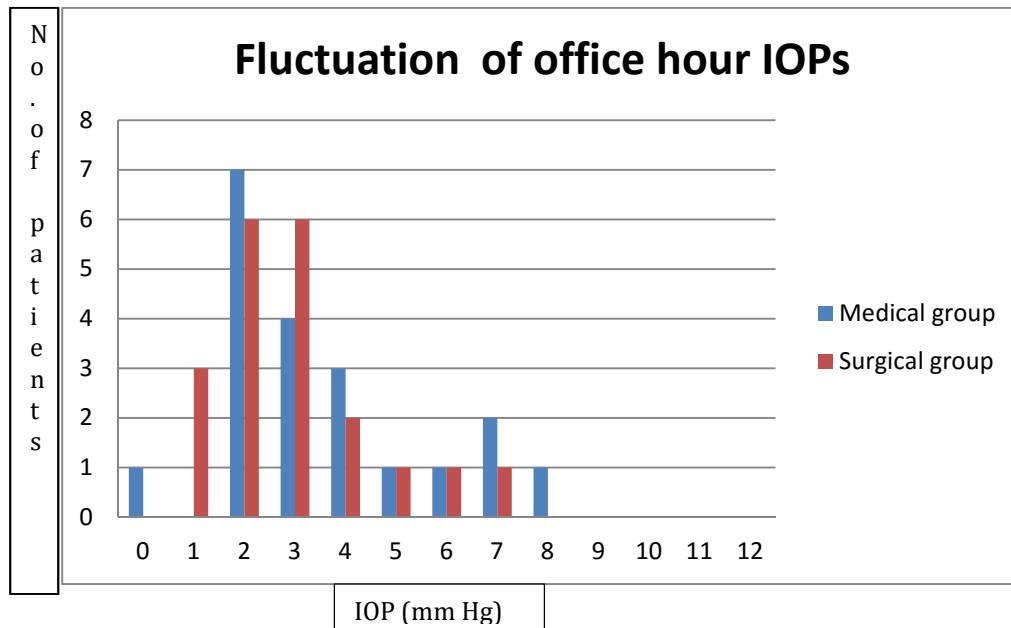
19 out of 20 in the surgical group had  $\leq 6$  mmHg variation in IOP. Only 1 had IOP variation as much as 10mm Hg.

In comparison, 13 out of the 20 in the medical group had  $\leq 6$  mmHg variation in IOP. 7 patients had IOP fluctuation of more than 6mm Hg.

### Fluctuation of IOP during office hours in individual patients in the two groups:

Figure 7 shows the details of the amount of fluctuation of IOP during office hours in the individual patients in the two groups

**Figure 7: Graph showing the office hour fluctuation of intraocular pressure versus the number of patients in the medical and surgical groups**

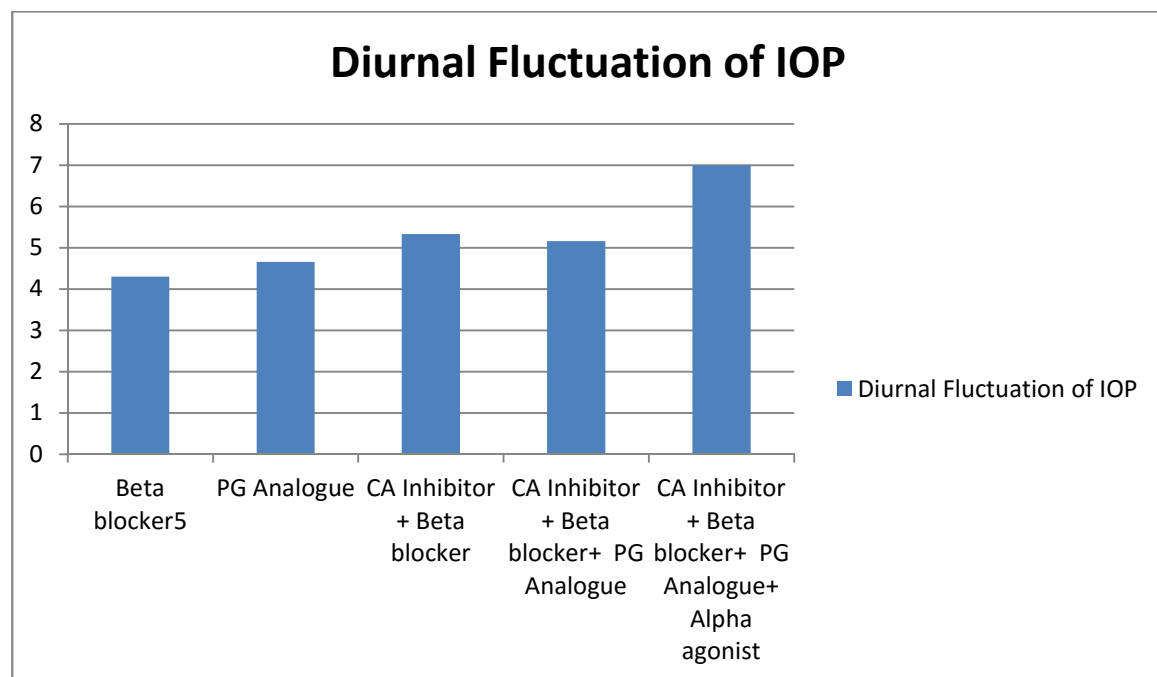


Variations in office hour IOP recordings (10 am, 2 pm and 6 pm measurements) showed greater similarity among the two groups. Only 3 patients in the medical group and 1 patient in the surgical group showed office hour variations more than 6 mm Hg.

## 24 hour IOP fluctuations among patients in the medically treated group on different anti-glaucoma medications:

Figure 8 shows the details 24 hour IOP fluctuations among patients in the medically treated group on the different anti-glaucoma medications

**Figure 8: The diurnal IOP fluctuation in the medical group among patients treated with different anti-glaucoma medications**



The numbers of patients of various anti-glaucoma medications were too small to make any statistically significant conclusions. However, among these patients fluctuation of IOP was similar in patients on various anti-glaucoma medications except patients on topical CA inhibitor, beta blocker, PG analogue and alpha agonist. However there were only two patients on these medications.

## DISCUSSION

40 eyes of 22 patients were recruited for this study, 20 in the medical arm and 20 in the surgical arm. There were more males in the medical group and females in the surgical group. This is unlikely to affect the outcome as gender has not been found to have any effect on open angle glaucoma.(1)

Patients with Primary Open Angle Glaucoma (POAG) or Pseudoexfoliation glaucoma (PEX Glaucoma) were recruited in this study. Patients with normal tension glaucoma (NTG) were not included in this study as the pathology in NTG is believed to be different from that in primary open angle glaucoma. Perfusion of the optic nerve head and retinal nerve fibre layer is thought to play an important role in the pathogenesis of NTG. Also since the initial baseline pressures are lower in NTG, further evaluation of the variation in IOP after initiation of treatment may not yield statistically significant conclusions. Systemic hypertension with nocturnal hypotension, migraine headaches and previous systemic blood loss are among important risk factors.(2) Systemic beta blockers are prone to cause nocturnal hypotension and thus play a role in the progression of normal tension glaucoma.(3) In this study, two patients with POAG on oral beta blockers have been recruited. However, only those with 30% reduction in IOP were recruited, and since patients were on anti hypertensive medication both prior to and after the initiation of treatment for glaucoma, the use of systemic anti hypertensive is unlikely to affect the outcomes of the study.



Both surgical and medical groups had 18 eyes with POAG and 2 eyes with PEX Glaucoma. Those on medical management were on various anti glaucoma medications, including topical carbonic anhydrase inhibitors, beta blockers, prostaglandin analogues, alpha agonists and various combinations of the above. The numbers in each subgroup were too small for further sub- group analysis.

The variation of intraocular pressure in glaucoma patients has been examined in various studies. Peaks in IOP outside office hours in nocturnal periods can go undiagnosed in as many as 45% of patients.(4) Hence, we measured IOP variation by 24 hour phasing. The intraocular pressure (IOP) was recorded at 6 time points- 10 am, 2 pm, 6 pm, 10 pm, 2 am, and 6 am. Goldmann Applanation Tonometry (GAT) was used for all measurements since it is the gold standard. However, Tonopen was used in addition to GAT during the 2am and 6 am recordings since the habitual supine posture in this time interval may affect IOP. At 2am and 6am Tonopen IOP was first measured at the patient's bedside followed by seated GAT IOP measurement 5 minutes later. The longer duration of supine position from around midnight to 6am may affect the IOP rather than the short durations of change in posture (as during measurement of supine Tonopen IOP and seated GAT IOP 5 minutes later in our study) as shown in some studies (5,6). In order to ensure comparability, we also measured Tonopen IOP at each time point in the patient's habitual position (seated). Also, since the daytime recordings were done using both GAT and Tonopen, with the patient in the same position, it allowed us to look for any inter device variation of IOP.

The pre treatment IOPs as well as the post treatment IOPs were similar in the two groups (Tables 4 and 5). Though the surgical group achieved greater reduction (51.5%) from the baseline IOP, as compared to the medical group (43.9%), the difference was not

statistically significant ( $p=0.880$ ). Also, when a sub analysis was performed comparing the patients in the medical group who had achieved reduction in IOP similar to the patients in surgical group, there was no difference (Figure 2). However, the numbers are too small to achieve statistical significance.

To assess inter device differences between GAT and Tonopen, we compared the IOPs measured by the two devices (Table 6). At all time points, there was no statistically significant difference between the two sets of measurements. However, at all time points, the Tonopen IOP was lower than GAT IOP in the medical group. In the surgical group, the values were nearly similar though Tonopen IOPs were slightly lower at fewer time points as compared to the medical group. We cannot provide any reason why the medical group had lower Tonopen IOP values. These values were seen not to be related to posture, since the daytime recordings also showed similar lower Tonopen values as compared to GAT. However none of these differences were statistically significant.

The mean peak IOP was found to be higher in the medical group when compared to the surgical group. However, this difference was not statistically significant. Additionally, it was found that 15 patients in the medically managed group had a peak IOP of more than or equal to 18 mm Hg, as compared to 5 patients in the surgically managed group. A study by Konstas et al(7) comparing patients on topical anti glaucoma medication with those who had undergone trabeculectomy found similar results. In their study, 11 medically controlled patients and none of the surgically managed patients had a peak IOP  $\geq 18$  mm Hg.

The mean 24 hour IOP in the surgically managed group was slightly lower than that of the medical group. This could be due to the baseline in the surgical group itself being lower,

though this was not statistically significant. Similar findings have been reported in other studies.(7,16)

On comparing the 24 hour phasing curves between the 2 groups, we found almost no fluctuation in IOP throughout the 24 hours in the surgical group ( $< 1$  mm Hg). Though some studies(8,9) have shown less fluctuation with surgery as compared to medical management, such low fluctuations as seen in our study have not been reported. This could be explained probably due to the large IOP reduction in IOP achieved (50%) in the surgical group, though for recruitment into the study, the required IOP reduction from baseline was 30%.

It is to be noted that the 24 hour curve was representative of the mean IOP of all patients at each time point.

On the other hand, the medical group showed peaks and troughs in the diurnal curve, with the maximum IOP being recorded at 6 am, and a smaller peak at 2 pm. This is similar to the early morning peaks described in a few other studies.(11) However, most other studies have shown a nocturnal peaking in IOP in patients on medical management.(12,13) It was also found in most studies that prostaglandins were probably the only class of medication that blunt the nocturnal peaks.(14,15) However, in our study, we did not have a pre treatment phased 24 hour recording which would have made better insight into the pattern of fluctuation prior to and after treatment. This was beyond the scope of the study, since the aim of the study was to compare the 24 hour IOP variations in surgically and medically treated patients.

Studies performed in patients with POAG have shown peaks in the early morning hours, followed by a trough and a second smaller peak later in the evenings. After

the initiation of medical management, it is likely that there is a persistence of the same pattern, albeit with a reduction in the IOP. However, this conclusion was derived from the graph representing the mean IOP value of all patients at each time point. On examining individual curves, it was found that out of the 20 patients in the medically managed arm, it was found that 5 patients had peak IOP at 6 am, and 5 at 2 am. It was also noted that 6 patients in the medical group had very similar IOPs (within 1 mm Hg) at 2 am and 6 am.

The fluctuation in each patient was calculated and the mean fluctuation arrived at. It was found that the fluctuation in the surgical group varied from 2.34 to 6.16 mm Hg, and the mean fluctuation was 4.25 mm Hg in the surgical group. Similarly, the range of fluctuation in the medical group was 4.03 to 7.97 mm Hg, with the mean being 6 mm Hg. Though the surgical group showed lesser fluctuation (Table 8), this was not statistically significant ( $p=0.129$ ). On plotting the fluctuation during office hours, nocturnal hours and throughout the 24 hour phasing curves in the groups, fewer patients had fluctuations  $> 6$  mm Hg in the surgical group as compared to the medical group, though not statistically significant. (Figure 6) These values mirror those reported in other 24 hour IOP studies, for instance, those by Konstas et al(7) and Klink et al(16). Also, for both the medical and surgical groups, the office hour fluctuations were found to be lower than the 24 hour fluctuations (Table 9).

It has been observed that there are nocturnal IOP peaks in glaucomatous patients. This could be due to various mechanisms- ocular perfusion, supine posture causing increased episcleral venous pressure, nocturnal hypotension, circulating catecholamines, etc. Even after the initiation of treatment, such nocturnal peaks have been seen with anti glaucoma medication.(17) In a study by Medeiros et al(9), no nocturnal peaks were found in

surgically treated patients. Studies have been performed in sleep labs. In our study we looked at the nocturnal IOP in supine position by recording the supine IOP measurements by Tonopen at 2 am and 6 am, during which time the patient would have been in recumbent position habitually.

In our study too, we saw that in the medical group, the IOP tended to rise at night from 10pm till the early morning peak at 6am (Figure 1). Hence the nocturnal rise persisted in the medical group. Thus it seems that in the medical group, though there is an overall reduction in IOP, the pattern of late night and early morning rise in IOPs which could be related to supine posture tended to persist. Also due to the small number of patients in each category of ant-glaucoma medications, subgroup analysis according to the different medications was not possible.

This is in contrast to the surgical group where the IOP was low at all times with no rise in IOP noted at the nocturnal habitual supine position recordings. However since various mechanisms are involved in the pathogenesis of nocturnal spikes we can only conclude that surgery blunts the nocturnal rise- which could be related to posture. This is similar to that observed in few other 24 hour phasing studies that have examined surgically managed patients, and found that there is no nocturnal IOP peak.(7) .

We also looked at the seated GAT IOP measurements in all patients at 2am and 6am , taken 5 minutes after the supine IOP measurements were taken with the Tonopen . The GAT recordings were similar to the Tonopen recordings though the GAT values were slightly higher than the corresponding Tonopen measurements. This was similar to that seen during other similar recordings during daytime (Table 6), indicating inter device difference rather than the effect of short term change in posture. This suggests that prolonged postural

positions are required to affect IOP, and that short term changes in posture are unlikely to affect IOP.

## SUMMARY AND CONCLUSIONS

1. In patients with open angle glaucoma with adequately controlled intraocular pressures, the surgically managed patients showed lower peak and mean intraocular pressures during 24-hour phasing as compared to those on anti-glaucoma medications. However these differences were not statistically significant.

It was found that 15 patients in the medically managed group had a peak IOP of more than or equal to 18 mm Hg, as compared to 5 patients in the surgically managed group.

2. During office hours as well as 24 hour phased IOP measurements, there was less fluctuation in IOP in the surgical group as compared to the medical group, though the difference was not statistically significant.

On examining individual data, only 1 out of 20 patients in the surgical group had a diurnal fluctuation of more than 6 mm Hg, as compared to 7 patients in the medical group.

3. The 24 hour IOP curve of the surgical group did not show any peak in the IOP at any time point throughout the 24 hour phased measurements. In the medical group, the 24 hour diurnal IOP plot showed higher IOPs during the nocturnal and early morning hours (2 am and 6 am).

The trend to higher nocturnal and early morning pressure in the medical group could be due to their normal diurnal variation pattern which would likely

have been seen prior to treatment as well. This in turn could be related to posture or haemodynamic factors. It is likely that the anti glaucoma medications have reduced the IOP overall, with the fluctuation pattern persisting post- treatment. Surgery seems to blunt any sort of diurnal variation which is expected in all patients including glaucomatous and normal individuals. But we could not find any plausible explanation for this and the exact mechanism needs to be elucidated. However, pre treatment diurnal curves were not available for comparison.

4. Immediate or short term change in posture (as measured by supine IOP recordings with Tonpen followed 5 minutes later by GAT recordings in seated posture) did not affect IOP measurements. Hence GAT measurements taken during nocturnal hours after waking a patient from habitual supine position can be used for studying IOP recordings at these times.
5. Similar to the low nocturnal IOPs seen in the surgical group in our study, few studies have reported low nocturnal IOPs in medically managed patients treated with prostaglandin analogues or fixed dose combinations of dorzolamide and timolol. Subgroup analyses of patients on these medications were not possible, due to very small numbers in this study. Studies with larger numbers of patients in each subgroup would be needed for comparison of their 24 hour IOP profiles with the surgically managed group.



## LIMITATIONS

1. It would have been ideal to have the pre treatment baseline diurnal 24 hour phasing curves of medically and surgically controlled patients, for comparison post treatment.

However, this was not planned as part of study design due to constraints of time.

2. While performing nocturnal IOP measurements, measuring Tonopen IOP in the seated position at 2 am and 6 am would have been ideal (in addition to the supine Tonopen readings and seated GAT readings at the same timings). This would have ensured better comparability of the seated and supine IOP measurements.

## ANNEXURES

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## INFORMATION SHEET

### **Diurnal intra ocular pressure profiles in patients with open angle glaucoma who have undergone trabeculectomy versus those on topical ocular hypotensive medications**

Name of participant:

You are invited to take part in this study. The information in this document is meant to help you decide whether or not to take part in the study. Please feel free to ask if you have any queries or concerns.

What is the study about?

Glaucoma is a disease of the eye in which there is damage to the nerve of the eye, causing gradual loss of vision from the sides of the eye or peripheries, also known as visual field defect. It does not usually have any symptoms in the early stages, and is usually detected when the vision loss affects the centre of the retina, or macula. At this point the vision loss is irreversible. It is the second leading cause of blindness in the world and the leading cause of irreversible blindness. Multiple factors have been thought to play a role in the disease, but a raised intra-ocular pressure (IOP, or the pressure within the eye) has been found to be the only factor that can be changed. A reduction in IOP has been found to slow/stop the progression of the disease.

Glaucoma can be treated with eyedrops or surgery. It has been found that intra-ocular pressure varies throughout the day in those with and without glaucoma. In patients with glaucoma, who have been treated with medication or surgery, normal follow up is done by checking IOP measurements in the hospital outpatient department (OPD). This may not give an accurate idea of the changes in pressure over the day. Hence, with your help, we would like to determine how much the IOP varies throughout the day.

As a part of the study, you will be hospitalized for one day, during which

time the intraocular pressure will be checked in both eye, by two different methods, six times. You are advised to continue any routine medication you are on at this time. There may be minimal discomfort associated with this. In this study, we will check the intra-ocular pressures at regular intervals throughout the day in two groups of individuals with open angle glaucoma- those who are on anti glaucoma eye drops and those who have undergone surgery for pressure control. We hope to detect IOP peaks and the importance of variation of IOP in glaucoma progression, and to compare whether surgery or glaucoma medication is more effective in controlling the peak IOP.

If you take part, what will you have to do?

If you take part in the study, you will be asked a few questions which are relevant to the study. Any medication that you are already on will be continued as usual. You will be admitted for a day in the in-patient wards of the department, and your eye pressure will be measured by two devices, in seated position at 10:00am, 2:00pm, 6:00pm, 10:00pm and in seated and lying down positions at 2 am and 6 am. You will be discharged the following day, and any further investigations will be done as per requirement on out- patient basis. Any change in diagnosis will be informed to you, and any change in long-term management plan will be instituted immediately.

Are there any risks for you if you take part in the study?

As a result of repeated intra-ocular pressure measurements, you may have some erosions on the surface of your cornea that may cause discomfort. To avoid this you will be administered lubricating eye drops after each IOP measurement, and followed-up in the out-patient department till the condition heals completely free of cost. We do not expect any long-term or serious ocular side-effects as a result of participation in this study, but if you do develop any other ocular side effects or problems due to the study, these will be treated at no cost to you. However, we are unable to provide any monetary compensation.

Do you have to pay?

You will have to pay only for the tests that are required for the routine management of your disease. All additional investigations for the study will be done free of cost.

What are the benefits to you if you take part in the study?

If you participate in the study, you will develop a greater understanding of glaucoma and the importance of IOP control. Also, the adequacy of current treatment can be assessed. If the medication you are on or surgery that you have undergone is found to be inadequate in controlling your IOP fully, you will be referred to glaucoma specialists for adequate revision of medication or surgery. This will ultimately help in slowing the progression of disease.

What are the possible benefits to other people?

The results of this study may provide benefit to the society in terms of advancement of medical knowledge, disease prevention, and therapeutic benefit to future patients. We hope that this study will help us determine the intra-ocular pressure variation profile in our population, and thereby decide an effective protocol for thorough work-up towards a precise diagnosis.

What will happen if I withdraw from the study?

There will be no adverse consequences of withdrawing from the study and there will be no disturbances in your routine eye care. Participation in the study is entirely voluntary and you may withdraw at any time.

## CONSENT FORM

**Study title:** Diurnal intra ocular pressure profiles in patients with open angle glaucoma who have undergone trabeculectomy versus those on topical ocular hypotensive medications

**Study Number:** \_\_\_\_\_

**Subject's Name:** \_\_\_\_\_

**Date of Birth / Age:** \_\_\_\_\_

- (i) I confirm that I have read and understood the information sheet dated \_\_\_\_\_ for the above study and have had the opportunity to ask questions. [ ]
- (ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]
- (iii) I understand that the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]
- (iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). [ ]
- (v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable

Signatory's Name: \_\_\_\_\_

Signature:

(Or) 

Representative: \_\_\_\_\_

Date: \_\_\_\_/\_\_\_\_/\_\_\_\_

Signatory's Name: \_\_\_\_\_

Signature of the Investigator: \_\_\_\_\_

Date: \_\_\_\_/\_\_\_\_/\_\_\_\_

Study Investigator's Name: \_\_\_\_\_

Signature or thumb impression of the Witness: \_\_\_\_\_

Date: \_\_\_\_/\_\_\_\_/\_\_\_\_

Name of the Witness: \_\_\_\_\_



## DATA COLLECTION SHEET

Date of examination:

Name:

Study Serial Number :

Age:

Schell Hospital Number :

Gender:

CMC Hospital number, if any:

Contact number:

Address:

### General History

Systemic illness: Diabetes mellitus- Y/N

Hypertension- Y/N

If hypertensive, medications on:

### Ocular history:

	Right eye	Left eye
Primary Ocular diagnosis (Type of Open angle glaucoma, phakic vs pseudophakic)		
Treatment given ( medical or surgical)		
Details of medication (If on topical ocular hypotensive medication- name and timings of medication)		

**Current (or most recent) findings (with date):**

	Right eye	Left eye
Visual fields		
Optic disc findings		
Day DVT/ Office hour IOP		
Central Corneal Thickness		

**Diurnal IOP Measurements** (corrected)

	RIGHT	EYE	LEFT	EYE
IOP	Tonopen	GAT	Tonopen	GAT
6 am				
10 am				
2 pm				
6 pm				
10 pm				
2 am				

## EXCEL DATA SHEETS

Obs No.	Gender	Hosp. No.	Hypertension	Type of glaucoma	Treatment type	R Tono 6 am	R GAT 6 am	L Tono 6 am	L GAT 6 am
1	2	535519s	1	1	2	12	13	15	17
2	2	535519s	1	1	1	12	13	15	17
3	2	547500s	1	2	2	14	15	19	19
4	2	547500s	1	2	1	14	15	19	19
5	2	528642s	1	2	1	18	20	13	15
6	2	528642s	1	2	2	18	20	13	15
7	1	496653s	2	1	2	7	7	9	9
8	1	496653s	2	1	2	7	7	9	9
9	2	500706s	2	1	1	17	20	20	22
10	2	500706S	2	1	1	17	20	20	22
11	1	490507s	2	1	2	9	10	16	20
12	1	448181s	2	1	2	14	16	15	16
13	1	448181s	2	1	1	14	16	15	16
14	1	380098s	1	1	1	10	14	10	13
15	1	380098s	1	1	1	10	14	10	13
16	1	551981s	1	1	2	13	15	10	11
17	1	551981s	1	1	1	13	15	10	11
18	1	496434s	1	1	1	14	14	10	10
19	1	496434s	1	1	2	14	14	10	10
20	1	234274s	2	1	1	12	10	10	13
21	2	563980s	2	1	2	12	10	16	18
22	2	563980s	2	1	1	12	10	16	18
23	1	536863s	1	1	1	15	17	18	18
24	1	536863s	1	1	1	15	17	18	18
25	2	228372s	2	1	2	21	19	20	20
26	2	228372s	2	1	2	21	19	20	20
27	2	542121s	2	1	1	18	20	14	14
28	2	542121s	2	1	2	18	20	14	14
29	2	570582s	2	1	1	15	16	11	10
30	2	570582s	2	1	2	15	16	11	10
31	2	545885s	2	1	2	9	12	13	16
32	2	545885s	2	1	1	9	12	13	16
33	2	477633s	2	1	2	10	12	10	10
34	2	477633s	2	1	2	10	12	10	10
35	2	526509s	2	1	2	11	11	12	12
36	2	526509s	2	1	2	11	11	12	12
37	1	477919s	1	1	1	12	15	10	13
38	1	477919s	1	1	1	12	15	10	13
39	1	516171s	1	1	2	14	12	13	13
40	1	836674e	1	1	1	19	21	20	22

Obs No.	Gender	Hosp. No.	R Tono 10 am	R GAT 10 am	L Tono 10 am	L GAT 10 am	R Tono 2 pm	R GAT 2 pm	L Tono 2 pm	L GAT 2 pm
1	2	535519s	14	13	17	19	19	18	12	12
2	2	535519s	14	13	17	19	19	18	12	12
3	2	547500s	11	10	13	14	12	13	14	14
4	2	547500s	11	10	13	14	12	13	14	14
5	2	528642s	11	13	9	11	18	19	11	13
6	2	528642s	11	13	9	11	18	19	11	13
7	1	496653s	7	9	9	11	10	10	10	10
8	1	496653s	7	9	9	11	10	10	10	10
9	2	500706s	9	12	13	14	11	13	15	16
10	2	500706S	9	12	13	14	11	13	15	16
11	1	490507s	10	12	18	20	12	15	19	21
12	1	448181s	12	14	16	18	9	11	16	16
13	1	448181s	12	14	16	18	9	11	16	16
14	1	380098s	12	13	10	11	9	14	11	15
15	1	380098s	12	13	10	11	9	14	11	15
16	1	551981s	11	13	10	11	14	16	16	17
17	1	551981s	11	13	10	11	14	16	16	17
18	1	496434s	18	20	12	10	22	21	11	12
19	1	496434s	18	20	12	10	22	21	11	12
20	1	234274s	8	12	7	10	11	14	14	15
21	2	563980s	11	10	14	14	12	12	14	16
22	2	563980s	11	10	14	14	12	12	14	16
23	1	536863s	19	20	18	20	16	16	16	17
24	1	536863s	19	20	18	20	16	16	16	17
25	2	228372s	17	17	21	18	11	10	15	17
26	2	228372s	17	17	21	18	11	10	15	17
27	2	542121s	20	20	16	14	16	16	14	14
28	2	542121s	20	20	16	14	16	16	14	14
29	2	570582s	14	15	11	13	12	13	12	10
30	2	570582s	14	15	11	13	12	13	12	10
31	2	545885s	12	16	15	18	11	14	10	13
32	2	545885s	12	16	15	18	11	14	10	13
33	2	477633s	12	12	14	12	10	13	12	12
34	2	477633s	12	12	14	12	10	13	12	12
35	2	526509s	10	10	12	12	14	12	10	10
36	2	526509s	10	10	14	12	14	12	10	10
37	1	477919s	7	11	6	12	14	13	15	14
38	1	477919s	7	11	6	12	14	13	15	14
39	1	516171s	12	12	14	14	14	12	13	15
40	1	836674e	17	18	14	16	15	18	15	17

Obs No.	Gender	Hosp. No.	R Tono 6 pm	R GAT 6 pm	L Tono 6 pm	L GAT 6 pm	R Tono 10 pm	R GAT 10 pm	L Tono 10 pm	L GAT 10 pm
1	2	535519s	12	12	18	18	14	14	17	18
2	2	535519s	12	12	18	18	14	14	17	18
3	2	547500s	12	12	12	14	11	12	14	16
4	2	547500s	12	12	12	14	11	12	14	16
5	2	528642s	14	15	9	9	13	14	9	9
6	2	528642s	14	15	9	9	13	14	9	9
7	1	496653s	9	9	10	10	7	8	8	10
8	1	496653s	9	9	10	10	7	8	8	10
9	2	500706s	14	15	17	16	14	11	14	14
10	2	500706S	14	15	17	16	14	11	14	14
11	1	490507s	11	14	17	20	10	12	18	18
12	1	448181s	15	16	18	18	10	13	12	14
13	1	448181s	15	16	18	18	10	13	12	14
14	1	380098s	11	11	9	12	13	17	13	16
15	1	380098s	11	11	9	12	13	17	13	16
16	1	551981s	11	16	13	18	15	18	13	16
17	1	551981s	11	16	13	18	15	18	13	16
18	1	496434s	18	16	10	10	14	14	8	10
19	1	496434s	18	16	10	10	14	14	8	10
20	1	234274s	10	12	11	12	8	11	10	13
21	2	563980s	10	11	12	14	12	10	12	12
22	2	563980s	10	11	12	14	12	10	12	12
23	1	536863s	16	18	16	18	14	16	14	14
24	1	536863s	16	18	16	18	14	16	14	14
25	2	228372s	16	16	17	15	18	20	18	20
26	2	228372s	16	16	17	15	18	20	18	20
27	2	542121s	16	16	16	16	16	18	14	16
28	2	542121s	16	16	16	16	16	18	14	16
29	2	570582s	12	12	11	12	13	15	12	10
30	2	570582s	12	12	11	12	13	15	12	10
31	2	545885s	10	12	9	10	10	15	9	13
32	2	545885s	10	12	9	10	10	15	9	13
33	2	477633s	10	11	11	13	12	14	14	12
34	2	477633s	10	11	11	13	12	14	14	12
35	2	526509s	10	12	11	13	13	13	10	11
36	2	526509s	10	12	11	13	13	13	10	11
37	1	477919s	11	11	13	14	11	14	13	15
38	1	477919s	11	11	13	14	11	14	13	15
39	1	516171s	10	14	14	12	12	12	13	14
40	1	836674e	16	16	16	16	17	18	16	19

Obs No.	Gender	Hosp. No.	R tono 2 am	R GAT 2 am	L Tono 2 am	L GAT 2 am
1	2	535519s	15	18	17	20
2	2	535519s	15	18	17	20
3	2	547500s	12	14	18	14
4	2	547500s	12	14	18	14
5	2	528642s	19	21	13	13
6	2	528642s	19	21	13	13
7	1	496653s	6	8	8	10
8	1	496653s	6	8	8	10
9	2	500706s	18	21	20	22
10	2	500706S	18	21	20	22
11	1	490507s	11	13	19	21
12	1	448181s	10	12	12	14
13	1	448181s	10	12	12	14
14	1	380098s	11	15	11	14
15	1	380098s	11	15	11	14
16	1	551981s	11	15	11	15
17	1	551981s	11	15	11	15
18	1	496434s	10	12	8	8
19	1	496434s	10	12	8	8
20	1	234274s	10	10	11	14
21	2	563980s	10	12	14	12
22	2	563980s	10	12	14	12
23	1	536863s	16	16	14	16
24	1	536863s	16	16	14	16
25	2	228372s	18	18	16	14
26	2	228372s	18	18	16	14
27	2	542121s	18	20	16	18
28	2	542121s	18	20	16	18
29	2	570582s	16	18	10	10
30	2	570582s	16	18	10	10
31	2	545885s	10	11	11	14
32	2	545885s	10	11	11	14
33	2	477633s	14	14	12	12
34	2	477633s	14	14	12	12
35	2	526509s	14	12	12	10
36	2	526509s	14	12	12	10
37	1	477919s	11	11	11	12
38	1	477919s	11	11	11	12
39	1	516171s	13	14	15	14
40	1	836674e	19	20	14	18

